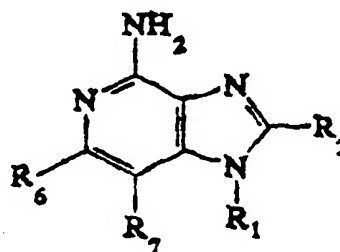




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US94/06891  <b>(22) International Filing Date:</b> 17 June 1994 (17.06.94)  <b>(30) Priority Data:</b> 08/092,002                      15 July 1993 (15.07.93)                      US  <b>(71) Applicant:</b> MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).  <b>(72) Inventors:</b> LINDSTROM, Kyle, J.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). NIKOLAIDES, Nick; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).  <b>(74) Agents:</b> REEDICH, Douglas, E. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> IMIDAZO[4,5-c]PYRIDIN-4-AMINES  <b>(57) Abstract</b>  Imidazo(4,5-c)pyridin-4-amines of formula (I) that induce interferon $\alpha$ biosynthesis in human cells. Also disclosed are pharmaceutical compositions containing such compounds and methods of inducing interferon $\alpha$ biosynthesis involving the use of such compounds and treatment of viral infections.		



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## IMIDAZO[4,5-c]PYRIDIN-4-AMINES

5                    Background of the InventionField of the Invention

This invention relates to imidazopyridine compounds and to intermediates in their preparation. In another aspect this invention relates to  
10 immunomodulator compounds and to antiviral compounds.

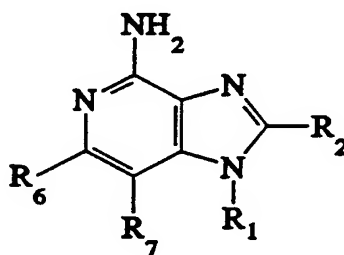
Description of the Related Art

Certain 1H-imidazo[4,5-c]quinolin-4-amines and methods for their preparation are known and disclosed,  
15 e.g., in U.S. Pat. Nos. 4,689,338, 5,037,985, and 5,175,296, EP-A 90.301766.3, PCT/US91/06682, PCT/US92/01305, and PCT/US92/07226 (Gerster), and U.S. Pat. No. 4,988,815 (Andre et al). Such compounds are said to have antiviral activity and certain of them are  
20 said to induce the biosynthesis of cytokines such as interferon. Certain 6'-C-alkyl-3-diazanepianocin derivatives, some of which are imidazo[4,5-c]pyridin-4-amines, are known and disclosed in EP-A 0510260 A2 (Obara et al.). These compounds are said to have  
25 antiviral activity.

Further compounds having antiviral or immunomodulator activity may advance the fields of antiviral therapy and immunomodulator therapy.

### Summary of the Invention

This invention provides compounds of Formula I:



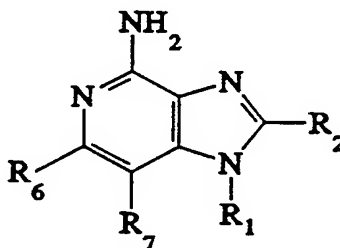
10 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>6</sub>, and R<sub>7</sub> are defined below.

This invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a  
15 pharmaceutically acceptable vehicle.

This invention also provides a method of inducing interferon biosynthesis in an animal, comprising the step of administering to said animal a compound of Formula I in an amount effective to induce said  
20 interferon biosynthesis, and a method of treating a viral infection in an animal comprising the step of administering to said animal a compound of Formula I in an amount effective to inhibit the viral infection.

### 25 Detailed Description of the Invention

The immunomodulator imidazo[4,5-c]pyridin-4-amines of this invention are compounds of the general Formula I:





$R_1$  is selected from the group consisting of hydrogen;  $CHR_xR_y$  wherein  $R_x$  is hydrogen and  $R_y$  is selected from the group consisting of straight chain, branched chain, or cyclic alkyl containing one to about  
5 ten carbon atoms, straight chain or branched chain alkenyl containing two to about ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to about six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four  
10 carbon atoms and the alkyl moiety contains one to about six carbon atoms, and phenylethyl; and  $-CH=CR_xR_y$  wherein each  $R_z$  is independently straight chain, branched chain, or cyclic alkyl of one to about six carbon atoms.

Preferred  $R_1$  substituents include 2-methylpropyl,  
15 n-butyl, 2-methyl-1-propenyl, ethoxyethyl, 2-hydroxy-2-methylpropyl, and 2-phenylethyl.

$R_2$  is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to about eight carbon atoms, straight  
20 chain or branched chain hydroxyalkyl containing one to about six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl,  
25 (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from the group consisting of methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to about four carbon atoms.

30 When  $R_2$  is alkyl it is preferably methyl, ethyl, propyl or butyl. When  $R_2$  is hydroxyalkyl it is preferably hydroxymethyl. When  $R_2$  is alkoxyalkyl, it is preferably ethoxymethyl.

$R_6$  and  $R_7$  are independently selected from the group  
35 consisting of hydrogen and alkyl of one to about five carbon atoms, with the proviso that  $R_6$  and  $R_7$  taken

together contain no more than six carbon atoms, and with the further proviso that when  $R_7$  is hydrogen then  $R_6$  is other than hydrogen and  $R_2$  is other than hydrogen or morpholinoalkyl, and with the further proviso that  
5 when  $R_6$  is hydrogen then  $R_7$  and  $R_2$  are other than hydrogen. Preferred  $R_6$  and  $R_7$  substituents include alkyl of one to about four carbon atoms, preferably methyl. Preferably both  $R_6$  and  $R_7$  are methyl.

Preferred compounds of the invention include:

- 10 2,7-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
2,6,7-trimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
4-amino- $\alpha,\alpha,2,6,7$ -pentamethyl-1H-imidazo[4,5-c]pyridine-1-ethanol;  
15 4-amino-2-butyl- $\alpha,\alpha,6,7$ -tetramethyl-1H-imidazo[4,5-c]pyridine-1-ethanol;  
4-amino-2-ethoxymethyl- $\alpha,\alpha,6,7$ -tetramethyl-1H-imidazo[4,5-c]pyridine-1-ethanol;  
20 1-(2-ethoxyethyl)-2,7-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine;  
2-butyl-7-ethyl-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride;  
2,6-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
25 2-ethyl-6,7-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
2,6,7-trimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
30 2-butyl-6,7-dimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride;  
6,7-dimethyl-1-(2-phenylethyl)-2-phenylmethyl-1H-imidazo[4,5-c]pyridin-4-amine;  
2,6-dimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
35 c]pyridin-4-amine;

2-ethoxymethyl-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;

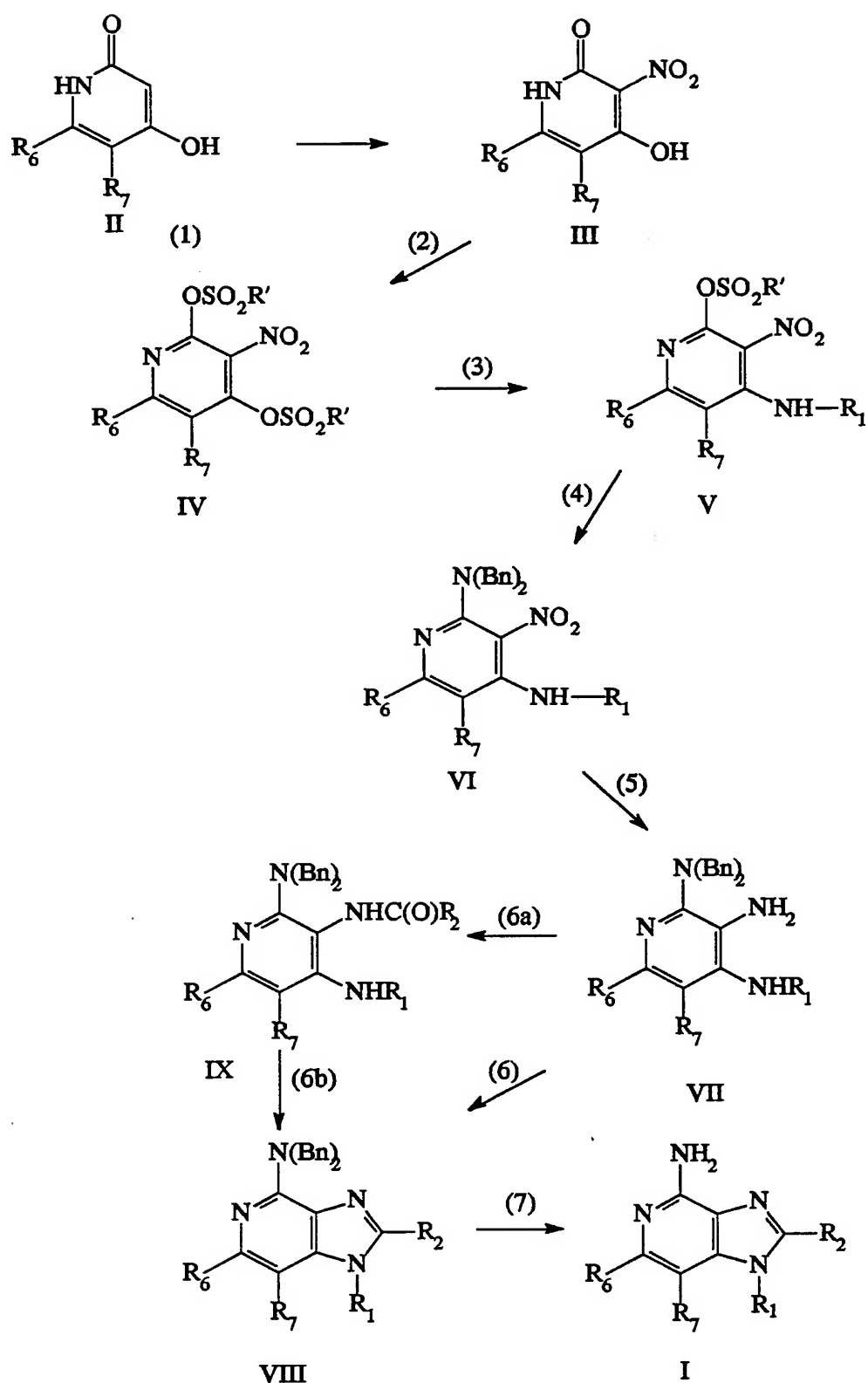
4-amino-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridine-2-methanol;

5 1-butyl-2,6-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine; and

2-butyl-6,7-dimethyl-1-(2-methyl-1-propenyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride.

10 Compounds of the invention can be prepared according to the Reaction Scheme, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>6</sub>, and R<sub>7</sub> are as defined above. Reaction Scheme I is particularly amenable to the preparation of compounds wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>6</sub>, and R<sub>7</sub> are selected from the  
15 preferred substituents enumerated above, and R' is alkyl (e.g., lower alkyl, i.e., alkyl of one to about four carbon atoms), perfluoroalkyl (e.g., perfluoro(lower)alkyl such as trifluoromethyl), aryl (e.g., phenyl), alkylaryl (e.g., (lower)alkylphenyl  
20 such as 4-methylphenyl), or haloaryl (e.g., halophenyl such as 4-bromophenyl).

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Reaction Scheme

The starting material for use in connection with Reaction Scheme I is a 4-hydroxy-2(1H)-pyridone of Formula II. Certain of these compounds are known. Others can be prepared readily by those skilled in the art, e.g., according to the general methods disclosed in J. Org. Chem., 1941, 6, 54, Tracy et al., J. Chem. Soc., 1962, 3638, Davis et al., Rel. Trav. Chim. 1944, 63, 231, Wibout et al., and Recueil, 1961, 80, 545, Salemink (incorporated herein by reference).

10 In step (1) of Reaction Scheme I, a compound of Formula II is nitrated under conventional nitration conditions, such as by heating (e.g., to 100°C) in the presence of nitric acid, preferably in a solvent such as acetic acid or as disclosed, e.g., in J. Heterocyclic Chem., 1970, 7, 389, Wang. Certain compounds of Formula III can be prepared directly (that is, without the need for nitration of a compound of Formula II) by base catalyzed condensation of a  $\beta$ -aminoester such as ethyl-3-aminocrotonate with a  
20 nitromalonate ester such as diethylnitromalonate (according to the general method disclosed, e.g., in J. Org. Chem. 1981, 46, 3040, Seeman et al., incorporated herein by reference).

In step (2) 3-nitropyridine-2,4-disulfonate of  
25 Formula IV is provided by reacting a compound of Formula III with a sulfonyl halide or preferably a sulfonic anhydride. Suitable sulfonyl halides include alkylsulfonyl halides such as methanesulfonyl chloride and trifluoromethanesulfonyl chloride, and arylsulfonyl  
30 halides such as benzenesulfonyl chloride, p-bromobenzenesulfonyl chloride, and p-toluenesulfonyl chloride. Suitable sulfonic anhydrides include those corresponding to the above-mentioned sulfonyl halides. A particularly preferred sulfonic anhydride is  
35 trifluoromethanesulfonic anhydride. Sulfonic anhydrides are preferred in view of the fact that the sulfonate anion generated as a byproduct of the

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reaction is a relatively poor nucleophile and as such does not give rise to undesired side products such as those in which the nitro group has been displaced.

Reaction conditions preferably involve first  
5 combining a compound of Formula III with a base, preferably an excess of a tertiary amine base (e.g., a trialkylamine base such as triethylamine) and preferably in an appropriate solvent such as dichloromethane and then adding the sulfonyl halide or  
10 the sulfonic anhydride. The addition is preferably carried out in a controlled fashion (e.g., dropwise) and at a reduced temperature (e.g., at about 0°C). The product can be isolated by conventional methods or it can be carried on without isolation as described below  
15 in connection with step (3).

Step (3) of the Reaction Scheme provides the product 3-nitro-4-(substituted)aminopyridine-2-sulfonates. Due to the presence of two sulfonate groups that could in principle be displaced, the  
20 reaction affords a mixture of products, which can be readily separated, e.g., by conventional chromatography techniques. The compound of Formula IV is reacted with an amine, preferably in the presence of an excess of a tertiary amine base in a solvent such as  
25 dichloromethane. Suitable amines include primary amines affording 4-substituted amino compounds of Formula V wherein the amino substituent is represented by R<sub>1</sub>. Preferred amines include those amines comprising the groups set forth above in connection with preferred  
30 R<sub>1</sub> substituents.

The reaction can be carried out by adding the tertiary amine base to the reaction mixture resulting from step (2), cooling to a reduced temperature (e.g., 0°C), and adding the amine in a controlled fashion  
35 (e.g., dropwise). The reaction can also be carried out by adding the amine to a solution of the compound of

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Formula IV and a tertiary amine base in a solvent such as dichloromethane. As the sulfonate is a relatively facile leaving group the reaction can be run at relatively low temperatures, e.g., about 0°C, and in  
5 relatively non-polar solvents (e.g., toluene) in order to decrease the amount of undesired 2-aminated and 2,4-diaminated side products. It is sometimes necessary or desirable to heat the reaction mixture after the addition in order to complete the reaction. The  
10 product can be isolated from the reaction mixture by conventional methods.

In step (4) the compound of Formula V is reacted with a hydrogenolyzable amine to afford a compound of Formula VI. The term "hydrogenolyzable amine" as used  
15 herein refers to any amine that is nucleophilic enough to displace the sulfonate group in step (4) and wherein the substituent or substituents can be removed by hydrogenolysis. Such amines are known to those skilled in the art to include arylmethyl amines and  
20 di(arylmethyl) amines, i.e., those amines wherein the substituent or substituents are identical or different from one another and with respect to each substituent the amino nitrogen is one carbon removed from an aromatic ring. The term "hydrogenolyzable amino  
25 substituent" as used herein refers to the substituent that obtains upon the use of a hydrogenolyzable amine in the reaction of step (4), i.e., a hydrogenolyzable amine absent one hydrogen atom. Primary hydrogenolyzable amines are less preferred, as their  
30 use provides an alternative site for cyclization in steps (6), (6a), or (6b) described below. Secondary hydrogenolyzable amines are preferred. Suitable secondary hydrogenolyzable amines include dibenzylamine (i.e., di(phenylmethyl)amine) and substituted  
35 derivatives thereof such as di[4-methyl-(phenylmethyl)]amine, di(2-furanylmethyl)amine, and the like. The Reaction Scheme specifically illustrates the

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process involving dibenzylamine. However, the reaction can be carried out with any suitable hydrogenolyzable amine.

The reaction of step (4) can be carried out by  
5 placing the starting material and the hydrogenolyzable amine in an inert solvent such as benzene, toluene, or xylene, and heating at a temperature and for a time sufficient to cause displacement of the sulfonate group by the hydrogenolyzable amine, such temperature and  
10 time being readily selected by those skilled in the art. The product can be isolated from the reaction mixture by conventional methods.

In step (5) the nitro group of a compound of Formula VI is reduced to an amino group. Methods for  
15 such a reduction are well known to those skilled in the art. A preferred method involves in situ generation of  $\text{Ni}_2\text{B}$  from sodium borohydride and  $\text{NiCl}_2$  in the presence of methanol. The compound of Formula VI is added to the reducing agent solution to effect reduction of the  
20 nitro group. The product can then be isolated by conventional methods.

In step (6) a compound of Formula VII is reacted with a carboxylic acid or an equivalent thereof to afford the cyclized compound of Formula VIII. Suitable  
25 equivalents to a carboxylic acid include acid halides, orthoesters, and orthoformates, acid halides, and carboxylic acids other than formic acid giving rise to 2-substituted products wherein the 2-substituent is represented by  $\text{R}_2$ . The reaction can be  
30 run in the absence of solvent or preferably in an inert solvent such as xylene or toluene in the presence of a carboxylic acid or equivalent (in the presence of an acid catalyst such as p-toluenesulfonic acid if  
35 80-150°C depending on the solvent if any) to drive off



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any alcohol or water formed as a side product of the reaction.

A compound of Formula VIII can also be prepared in two steps from a compound of Formula VII. The first  
5 step, represented by step (6a) of the Reaction Scheme, involves reacting the compound of Formula VII with an acyl halide of the formula  $R_2C(O)X$  wherein X is chloro or bromo and  $R_2$  is as defined above. The product of Formula IX can be isolated and then cyclized in step  
10 (6b) by reacting with methanolic ammonia.

In step (7) the cyclized compound of Formula VIII is hydrogenolyzed to afford the 4-amino compound. Conventional well known catalytic hydrogenation conditions are suitable. Preferred conditions involve  
15 heating in formic acid in the presence of  $Pd(OH)_2/C$ .

Certain compounds of the invention cannot be prepared readily according to the Reaction Scheme due to incompatibility of reagents with certain of the functional groups recited in connection with  $R_1$ ,  $R_2$ ,  $R_6$ ,  
20 and  $R_7$ . Such compounds, however, can be prepared by those skilled in the art using well known methods of functional group protection or manipulation, by appropriate adaptation of the synthetic methods disclosed in U.S. Pat. Nos. 4,988,815 (Andre), or by  
25 adaptations of the synthetic methods disclosed in U.S. Pat. Nos. 4,689,338, 5,037,985, and 5,175,296, EP-A 90.301766.3, PCT/US91/06682, PCT/US92/01305, and PCT/US92/07226 (Gerster), the relevant disclosures of each of these being incorporated herein by reference.

30 The product compound of Formula I can be isolated by the conventional means disclosed in U.S. Pat. No. 4,689,338 (Gerster), such as, for example, removal of the solvent and recrystallization from an appropriate solvent (e.g., N,N-dimethylformamide) or solvent  
35 mixture, by dissolution in an appropriate solvent (such as methanol) and re-precipitation by addition of a

second solvent in which the compound is insoluble, or by column chromatography.

A compound of Formula I can be used as an immunomodulating agent itself or it can be used in the form of a pharmaceutically acceptable acid-addition salt such as a hydrochloride, dihydrogen sulfate, trihydrogen phosphate, hydrogen nitrate, methanesulfonate or a salt of another pharmaceutically acceptable acid. A pharmaceutically acceptable acid-addition salt of a compound of Formula I can be prepared, generally by reaction of the compound with an equimolar amount of a relatively strong acid, preferably an inorganic acid such as hydrochloric, sulfuric, or phosphoric acid, or an organic acid such as methanesulfonic acid, in a polar solvent. Isolation of the salt is facilitated by the addition of a solvent, such as diethyl ether, in which the salt is insoluble.

A compound of the invention can be formulated for the various routes of administration in a pharmaceutically acceptable vehicle, such as water or polyethylene glycol, along with suitable adjuvants, excipients, and the like. Particular formulations can be readily selected by those skilled in the art. Suitable formulations for topical application include creams, ointments and like formulations known to those skilled in the art (e.g., formulations analogous to those disclosed in commonly assigned copending application 07/845,323, incorporated herein by reference). Parenteral formulations are also suitable (e.g., formulations analogous to those disclosed in EP-A-90.304812.0, incorporated herein by reference).

A pharmaceutical composition of the invention comprises a therapeutically effective amount of an imidazopyridin-4-amine. The amount that constitutes a therapeutically effective amount will depend on the particular compound, the particular formulation, the

route of administration, and the intended therapeutic effect. Those skilled in the art can determine a therapeutically effective amount with due consideration of such factors.

- 5       A number of compounds of Formula I were tested and found to induce biosynthesis of interferon in human cells. The test methods and results are set forth below. As a result of this immunomodulating activity the compounds exhibit antiviral and antitumor activity.
- 10   They can therefore be used to control viral infections as well as tumors. For example, a compound of Formula I can be used as an agent to control infections in mammals caused by Type II Herpes simplex virus. Compounds of Formula I can also be used to treat a
- 15   herpes infection by oral, topical, or intraperitoneal administration. The results below suggest that at least certain compounds of the invention might be useful in treating other diseases such as warts, Hepatitis B and other viral infections, cancer such as
- 20   basal cell carcinoma, and other neoplastic diseases.

In the following Examples, all reactions were run with stirring under an atmosphere of dry nitrogen unless otherwise indicated. The structures were confirmed by nuclear magnetic resonance spectroscopy.

25   The particular materials and amounts thereof recited in the Examples, as well as other conditions and details, should not be construed to unduly limit the invention.

#### Example 1

- 30       6-Methyl-3-nitropyridine-2,4-  
bis(trifluoromethanesulfonate)

Triethylamine (24.5 mL, 0.176 moles) was added to a mixture of 4-hydroxy-6-methyl-3-nitro-2(1H)-pyridinone (15 g, 0.088 mole) in methylene chloride

35   (700 mL). The reaction mixture was cooled to 5°C. Trifluoromethanesulfonic anhydride (50 g, 0.176 mole) was slowly added to the reaction mixture while

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maintaining the temperature below 15°C. After the addition was completed, the reaction mixture was stirred at 5°C for 15 minutes. The ice bath was removed and the reaction mixture was stirred for an additional 2 hours. The reaction mixture was diluted with water. The organic phase was separated, dried over magnesium sulfate, filtered through a layer of silica gel then concentrated under a stream of nitrogen to provide 32.4 g of solid. A portion (1.4 g) of this solid was recrystallized from petroleum ether to provide the desired product as a solid, m.p. 50-52°C. Analysis: Calculated for  $C_8H_4F_6N_2O_8S_2$ : %C, 22.13; %H, 0.93; %N, 6.45; Found: %C, 22.08; %H, 0.84; %N, 6.49.

15

## Example 2

6-Methyl-3-nitro-4-[(phenylethyl)amino]-2-pyridinyl trifluoromethanesulfonate

Triethylamine (10 mL) was added to a mixture of 6-methyl-3-nitropyridine-2,4-bis(trifluoromethanesulfonate) (31 g, 0.071 moles) in methylene chloride (300 mL). The reaction mixture was cooled in an ice bath. Phenethylamine (9 mL) was diluted with methylene chloride (50 mL) then slowly added to the reaction mixture. After the addition was completed, the reaction mixture was stirred with cooling for about 1 hour then at ambient temperature overnight. The reaction mixture was diluted with additional methylene chloride, washed twice with water, washed twice with aqueous sodium bicarbonate, dried over magnesium sulfate and then concentrated under vacuum to provide an orange liquid. This liquid was eluted through a layer of silica gel with methylene chloride then slurried with petroleum ether to provide 16 g of a yellow solid. A small portion (1 g) of this material was recrystallized twice from cyclohexane to provide the desired product as a solid m.p. 78-79°C. Analysis:

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Calculated for  $C_{15}H_{14}F_3N_3O_5S$ : %C, 44.45; %H, 3.48; %N, 10.37; Found: %C, 44.81; %H, 3.42; %N, 10.28.

## Example 3

5        6-Methyl-4-[(2-methylpropyl)amino]-3-nitro-2-pyridinyl trifluoromethanesulfonate

Triethylamine (8.34 mL, 0.06 mole) was added to a cooled (0°C) solution of 4-hydroxy-6-methyl-3-nitro-2(1H)-pyridinone (5.0 g, 0.03 moles) in methylene  
10 chloride (300 mL). Trifluoromethanesulfonic anhydride (10.1 mL, 0.06 moles) was added and the resulting mixture was stirred at 0°C for about 30 minutes. Isobutylamine (8.94 mL, 0.09 mole) was added and the reaction mixture was stirred for about 30 minutes. The  
15 reaction mixture was quenched with water (500 mL) then extracted with methylene chloride (3 x 50 mL). The extracts were combined, dried over magnesium sulfate then concentrated under vacuum to provide an orange oil. The oil was purified by silica gel column  
20 chromatography eluting with hexane:ethyl acetate (70:30) to provide 3.4 g of the desired product as a yellow solid.

## Example 4

25        4-[(2-Hydroxy-2-methylpropyl)amino]-5,6-dimethyl-3-nitro-2-pyridinyl trifluoromethanesulfonate

Triethylamine (1.2 mL, 8.69 mmole) was added to a suspension of 4-hydroxy-5,6-dimethyl-3-nitro-2(1H)-pyridinone (0.8 g, 4.3 mmole) in methylene chloride (25  
30 mL). The resulting solution was cooled in an ice bath. Trifluoromethanesulfonic anhydride (1.46 mL, 8.69 mmole) was added dropwise to the solution. After the addition was complete, the ice bath was removed and the reaction was allowed to warm to ambient temperature  
35 over a period of 30 minutes. The reaction mixture was filtered through a layer of silica gel then the silica gel was eluted with additional methylene chloride. The

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filtrate was concentrated under vacuum to provide 1.6 g (3.57 mmole) of 5,6-dimethyl-3-nitropyridine-2,4-bis(trifluoromethanesulfonate). This material was taken up in methylene chloride (30 mL) then cooled in an ice bath. 2-Hydroxyisobutylamine (0.32 g, 3.57 mmole) and triethylamine (0.5 mL, 3.57 mmole) were added to the cooled solution then the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with methylene chloride, washed with water, dried over magnesium sulfate and then concentrated under vacuum to provide a yellow oil. The oil was purified by silica gel column chromatography eluting with ethyl acetate:hexane (25:75) to provide 0.7 g of the desired product as a solid, m.p. 79-80°C.

Analysis: Calculated for  $C_{12}H_{16}F_3N_3O_6S$ : %C, 37.21; %H, 4.16; %N, 10.85; Found: %C, 37.47; %H, 4.13; %N, 10.89.

## Examples 5 - 9

Using the general method of Example 3, 4-hydroxy-3-nitro-2(1H)-pyridinones of Formula II were reacted first with trifluoromethanesulfonic anhydride then with an amine of formula  $R_1NH_2$  to provide the intermediates of Formula IV shown in Table 1.

Table 1						
Example Number	Intermediate of Formula II		Intermediate of Formula IV			
	R <sub>6</sub>	R <sub>7</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	
5	methyl	H	methyl	H	n-butyl	
6	methyl	methyl	methyl	methyl	2-phenylethyl	
7	methyl	methyl	methyl	methyl	2-methylpropyl	
8	chloro	methyl	chloro	methyl	2-methylpropyl	
9	chloro	methyl	chloro	methyl	1,1-dimethylethyl	

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## Example 10

N<sup>4</sup>-Butyl-6-methyl-3-nitro-N<sup>2</sup>,N<sup>2</sup>-

bis(phenylmethyl)pyridine-2,4-diamine

Dibenzylamine (1.04 g, 5.28 mmole), triethylamine (0.53 g, 5.28 mmole), 4-butylamino-6-methyl-3-nitro-2-pyridinyl trifluoromethanesulfonate (1.72 g, 5.28 mmole) and toluene (45 mL) were combined and heated at reflux for 18 hours. The reaction mixture was cooled to ambient temperature then filtered through a layer of silica gel. The silica gel was eluted with methylene chloride. The combined organic filtrates were evaporated to provide 2.08 g of an oily semisolid.

## Examples 11 - 17

Using the general method of Example 10, the intermediates of Formula V shown in Table 2 were prepared by reacting the indicated intermediate of Formula IV with dibenzylamine.



Table 2

Example Number	Intermediate of Formula IV Example	Intermediate of Formula V		
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>
11	2	methyl	H	2-phenylethyl
12	3	methyl	H	2-methylpropyl
13	4	methyl	methyl	2-hydroxy-2-methylpropyl
14	6	methyl	methyl	2-phenylethyl
15	7	methyl	methyl	2-methylpropyl
16	8	chloro	methyl	2-methylpropyl
17	9	chloro	methyl	1,1-dimethylethyl

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## Example 18

6-Methyl-N<sup>4</sup>-(2-methylpropyl)-N<sup>2</sup>,N<sup>2</sup>-

bis(phenylmethyl)pyridine-2,3,4-triamine

Sodium borohydride (585 mg, 16 mmole) was added to a solution of nickel (II) chloride hydrate (1.02 g, 4.3 mmole) in methanol (100 mL). The addition caused a black solid to form along with gas evolution. The resulting heterogeneous mixture was stirred at ambient temperature for 30 minutes. A solution containing 6-methyl-N<sup>4</sup>-(2-methylpropyl)-3-nitro-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,4-diamine (3.47 g, 8.6 mmole) in methylene chloride (20 mL) was added followed by the addition of sodium borohydride (1.37 g, 36 mmole). The reaction mixture was stirred at ambient temperature for about 30 minutes then eluted through a layer of silica gel with a methanol/methylene chloride mixture. The filtrate was concentrated under vacuum. The resulting residue was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried with magnesium sulfate and concentrated under vacuum to provide 2.74 g of the desired product as a green foam.

## Examples 19 - 25

Using the general method of Example 18, the intermediates of Formula VI shown in Table 3 were prepared by reducing the indicated intermediate of Formula V.

Table 3

Example Number	Intermediate of Formula V Example	Intermediate of Formula VI		
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>
19	10	methyl	H	n-butyl
20	11	methyl	H	2-phenylethyl
21	13	methyl	methyl	2-hydroxy-2-methylpropyl
22	14	methyl	methyl	2-phenylethyl
23	15	methyl	methyl	2-methylpropyl
24	16	chloro	methyl	2-methylpropyl
25	17	chloro	methyl	1,1-dimethylethyl

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## Example 26

N<sup>3</sup>-Acetyl-6-methyl-N<sup>4</sup>-(2-phenylethyl)-  
N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,3,4-triamine

Triethylamine (2 mL) was added to a solution of 6-methyl-N<sup>4</sup>-(2-phenylethyl)-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)-pyridine-2,3,4-triamine (6 g, 14.2 mmole) in methylene chloride (50 mL). Acetyl chloride (1.1 mL, 15.5 mmole) was slowly added to the reaction mixture which was then heated on a steam bath for about 1 hour. The reaction mixture was stirred at ambient temperature overnight then diluted with water and methylene chloride. The organic phase was separated, washed with water, dried over magnesium sulfate and then concentrated under vacuum to provide a light green solid. This solid was slurried with ethyl acetate/hexane then recrystallized from ethyl acetate/hexane to provide 4.1 g of a white solid. A small portion (0.8 g) was purified by silica gel column chromatography to provide the desired compound as a white solid, m.p. 152-153°C. Analysis: Calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O: %C, 77.56; %H, 6.94; %N, 12.06; Found: %C, 77.61; %H, 6.89; %N, 12.05.

## Examples 27 - 28

Using the general method of Example 26 except that the triethylamine was omitted, the intermediates of Formula VII shown in Table 4 were prepared by reacting the indicated intermediate of Formula VI with an acid chloride of formula R<sub>2</sub>C(O)Cl.

Table 4						
Example Number	Intermediate of Formula VI Example	Intermediate of Formula VII				
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	R <sub>2</sub>	
27	18	methyl	H	2-methylpropyl	methyl	
28	21	methyl	methyl	2-hydroxy-2-methylpropyl	ethoxymethyl	

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## Example 29

2,6-Dimethyl-1-(2-phenylethyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-  
1H-imidazo[4,5-c]pyridin-4-amine

N<sup>3</sup>-Acetyl-6-methyl-N<sup>4</sup>-(2-phenylethyl)-N<sup>2</sup>,N<sup>2</sup>-  
bis(phenylmethyl)pyridine-2,3,4-triamine (3.9 g, 8.39  
mmole) was combined with 12 wt % ammonia in methanol  
(40 mL), placed in a Parr bomb and heated at 150°C for  
5 hours. The resulting solid was collected then  
purified by silica gel column chromatography eluting  
with ethyl acetate:hexane (20:80) to provide 2.56 g of  
the desired product as a solid, m.p. 124-126°C.  
Analysis: Calculated for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>: %C, 80.68; %H, 6.77;  
%N, 12.55; Found: %C, 80.24; %H, 6.68; %N, 12.42.

## Examples 30 - 31

Using the general method of Example 29, the  
intermediates of Formula VIII shown in Table 5 were  
prepared by cyclizing the indicated intermediate of  
Formula VII.

Table 5					
Example Number	Intermediate of Formula VII Example	Intermediate of Formula VIII			
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	R <sub>2</sub>
30	27	methyl	H	2-methylpropyl	methyl
31	28	methyl	methyl	2-hydroxy-2-methylpropyl	ethoxymethyl

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## Example 32

6-Chloro-2,7-dimethyl-1-(1,1-dimethylethyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine

6-Chloro-5-methyl-N<sup>4</sup>-(1,1-dimethylethyl)-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,3,4-triamine was combined with an excess of triethyl orthoacetate and heated first on a steam bath for about 16 hours and then in an oil bath at 130°C for 2 hours. The excess triethyl orthoacetate was distilled off under vacuum. The resulting residue was diluted with methylene chloride, washed with water and sodium bicarbonate solution, dried over magnesium sulfate then filtered through a layer of silica gel eluting with additional methylene chloride. The filtrate was concentrated under vacuum to provide a mixture which was carried on to the next step.

## Example 33

6-Chloro-2,7-dimethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine

The material from Example 32 was diluted with toluene then combined with phosphorous oxychloride and heated at reflux overnight. The reaction mixture was concentrated under vacuum. The residue was diluted with water, basified with ammonium hydroxide then extracted several times with methylene chloride. The methylene chloride extracts were combined, dried over magnesium sulfate then concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with 10-40% ethyl acetate in hexane to provide the desired product.



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## Example 34

6-Chloro-1-(2-ethoxyethyl)-2,7-dimethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine Sodium iodide (1.5 g) and potassium carbonate (1 g) were added to a solution of 6-chloro-2,7-dimethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (1.0 g, 2.7 mmole) in acetone (250 mL). 2-Bromoethyl ethyl ether (0.5 mL, 4.4 mmole) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was partitioned between methylene chloride and water. The methylene chloride phase was separated, dried with magnesium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with 10-30% ethyl acetate in hexane to provide 0.7 g of the desired product.

## Example 35

1-n-Butyl-2,6-dimethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine N<sup>4</sup>-n-Butyl-6-methyl-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,3,4-triamine (0.65 g, 1.7 mmole) was combined with toluene (10 mL) and acetyl chloride (0.12 mL, 1.7 mmole) and stirred at ambient temperature for 15 minutes. Phosphorous oxychloride (0.31 mL) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was evaporated. The residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (70:30) to provide 0.18 g of the desired product.

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## Example 36

6,7-Dimethyl-1-(2-phenylethyl)-2,N<sup>4</sup>,N<sup>4</sup>-  
tris(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine

Phenylacetyl chloride (0.6 mL, 4.5 mmole) was added to a solution of 5,6-dimethyl-N<sup>4</sup>-(2-phenylethyl)-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,3,4-triamine (1.96 g, 4.5 mmole) in methylene chloride (100 mL) and the resulting mixture was stirred at ambient temperature overnight. A catalytic amount of p-toluenesulfonic acid was added and stirring was continued at ambient temperature over the weekend. The reaction mixture was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate then concentrated under vacuum to provide an oil. The oil was purified by silica gel column chromatography eluting with 5-10% ethyl acetate in hexane to provide 1.8 g of the desired product as a white solid, m.p. 139-141°C. Analysis: Calculated for C<sub>37</sub>H<sub>36</sub>N<sub>4</sub>: %C, 82.80; %H, 6.76; %N, 10.44; Found: %C, 82.86; %H, 6.78; %N, 10.36.

## Examples 37 - 43

Using the general method of Example 36, the intermediates of Formula VIII shown in Table 6 were prepared by reacting the indicated intermediate of Formula VI with an acid chloride of formula R<sub>2</sub>C(O)Cl.

Table 6

Example Number	Intermediate of Formula VI Example	Intermediate of Formula VIII			
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	R <sub>2</sub>
37	18	methyl	H	2-methylpropyl	phenylmethoxymethyl
38	21	methyl	methyl	2-hydroxy-2-methylpropyl	methyl
39	21	methyl	methyl	2-hydroxy-2-methylpropyl	n-butyl
40	22	methyl	methyl	2-phenylethyl	methyl
41	22	methyl	methyl	2-phenylethyl	n-butyl
42	23	methyl	methyl	2-methylpropyl	methyl
43	24	chloro	methyl	2-methylpropyl	methyl

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## Example 44

2-Ethyl-6,7-dimethyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine

Butyllithium (0.5 mL of 2.5 M in hexanes) was added to a cooled (-78°C) solution of 2,6,7-trimethyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (0.5 g, 1.2 mmole) in tetrahydrofuran (30 mL). The reaction mixture was allowed to warm to -10°C then it was cooled to -78°C and combined with methyl iodide (0.23 mL, 3.6 mmole). The reaction mixture was allowed to warm to ambient temperature then diluted with water and diethyl ether. The ether layer was separated, washed with ammonium chloride solution, dried over magnesium sulfate and then concentrated to provide 0.5 g of the desired product.

## Example 45

2,6-Dimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine

Palladium hydroxide on carbon (0.5 g, Pearlman's catalyst) was added to a mixture of 2,6-dimethyl-1-(2-phenylethyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (2.3 g, 5.15 mmole) in formic acid (10 mL). The reaction mixture was heated at reflux overnight. An additional 0.5 g of catalyst was added and refluxing was continued overnight. The reaction mixture was neutralized with saturated sodium bicarbonate solution, diluted with methanol then filtered through a layer of celite to remove the catalyst. The celite layer was flushed with methylene chloride and methanol. The filtrates were combined and concentrated under vacuum to provide a mixture of water and a solid. This mixture was extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate and concentrated under vacuum to

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provide 1.2 g of a tan solid. This solid was recrystallized from ethanol to provide 0.24 g of the desired product as a solid, m.p. 185-187°C. Analysis: Calculated for  $C_{16}H_{18}N_4$ : %C, 72.15; %H, 6.81; %N, 21.04; Found: %C, 71.51; %H, 6.88; %N, 20.61.

#### Examples 46 - 56

Using the general method of Example 45, the products of Formula I shown in Table 7 were prepared by hydrogenolizing the indicated intermediate of Formula VIII. The melting points and elemental analyses are shown in Table 8.

Table 7

Example Number	Intermediate of Formula VIII Example	Product of Formula I			
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	R <sub>2</sub>
46	30	methyl	H	2-methylpropyl	methyl
47	31	methyl	methyl	2-hydroxy-2-methylpropyl	ethoxymethyl
48	35	methyl	H	n-butyl	methyl
49	36	methyl	methyl	2-phenylethyl	phenylmethyl
50	37	methyl	H	2-methylpropyl	hydroxymethyl
51	38	methyl	methyl	2-hydroxy-2-methylpropyl	methyl
52	39	methyl	methyl	2-hydroxy-2-methylpropyl	n-butyl
53	40	methyl	methyl	2-phenylethyl	methyl
54	41	methyl	methyl	2-phenylethyl	n-butyl

Table 7					
Example Number	Intermediate of Formula VIII Example	Product of Formula I			
		R <sub>6</sub>	R <sub>7</sub>	R <sub>1</sub>	R <sub>2</sub>
55	42	methyl	methyl	2-methylpropyl	methyl
56	44	methyl	methyl	2-methylpropyl	ethyl

Table 8

Example Number	m.p. (°C)	Elemental Analysis							
		Formula	Calculated				Found		
			%C	%H	%N		%C	%H	%N
46	153-155	$C_{12}H_{18}N_4 + 0.15 H_2O$	65.21	8.35	25.35		65.38	8.41	25.37
47	178-181	$C_{13}H_{24}N_4O_2$	60.68	8.32	18.87		60.55	8.13	19.11
48	130-132	$C_{12}H_{18}N_4 + 0.2 H_2O$	64.95	8.36	25.25		65.01	8.10	24.9
49	170-173	$C_{23}H_{24}N_4 + 0.5 H_2O$	75.59	6.89	15.33		75.56	6.99	15.36
50	180-181	$C_{12}H_{18}N_4O + 0.33 H_2O$	59.99	7.83	23.32		59.87	7.7	23.39
51	249-250	$C_{13}H_{20}N_4O$	62.88	8.12	22.56		62.67	8.02	22.19
52	167-170	$C_{16}H_{26}N_4O + 0.75 H_2O$	63.07	9.10	18.39		63.40	8.75	18.33
53	142-145	$C_{17}H_{20}N_4 + 0.5 H_2O$	70.56	7.31	19.36		70.90	7.38	19.43
54	134-135	$C_{20}H_{26}N_4 + 0.2 H_2O$	73.67	8.16	17.18		73.92	8.21	17.32
55	157-159	$C_{13}H_{20}N_4 + 0.2 CH_2Cl_2$	63.59	8.25	22.47		63.37	8.18	22.27



Table 8								
Example Number	m.p. (°C)	Elemental Analysis						
		Formula	Calculated			Found		
			%C	%H	%N	%C	%H	%N
56	163-165	$C_{14}H_{22}N_4$	68.26	9.00	22.74	68.36	9.03	22.73

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## Example 57

1-(2-Ethoxyethyl)-2,7-dimethyl-  
1H-imidazo[4,5-c]pyridin-4-amine

6-Chloro-1-(2-ethoxyethyl)-2,7-dimethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (0.7 g, 1.56 mmole) was taken up in methanol saturated with anhydrous hydrochloric acid (100 mL), combined with palladium hydroxide on carbon and then hydrogenated on a Paar apparatus for four hours. The reaction mixture was filtered to remove the catalyst then concentrated under vacuum. The residue was partitioned between methylene chloride/water/sodium bicarbonate. The methylene chloride layer was separated, dried over magnesium sulfate then concentrated under vacuum to provide an off white solid. This material was recrystallized from ethyl acetate/hexane to provide 0.18 g of the desired product as a solid, m.p. 129-130°C. Analysis: Calculated for: C<sub>12</sub>H<sub>18</sub>N<sub>4</sub>O +  $\frac{1}{2}$ H<sub>2</sub>O: %C, 60.35; %H, 7.81; %N, 23.46; Found: %C, 60.64; %H, 7.50; %N, 23.39.

## Example 58

2,7-Dimethyl-1-(2-methylpropyl)-  
1H-imidazo[4,5-c]pyridin-4-amine

Using the general method of Example 57, 6-chloro-2,7-dimethyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (1 g, 2.3 mmole) was hydrogenolized to provide 0.07 g of the desired product as a solid, m.p. 178-180°C. Analysis: Calculated for C<sub>12</sub>H<sub>18</sub>N<sub>4</sub>: %C, 66.02; %H, 8.31; %N, 25.66; Found: %C, 65.58; %H, 8.34; %N, 25.30.

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## Example 59

6-Methyl-1-(2-methylpropyl)-2-morpholinomethyl-  
1H-imidazo[4,5-c]pyridin-4-amine

Part A

6-Methyl-N<sup>4</sup>-(2-methylpropyl)-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,3,4-triamine (2.27 g, 6.1 mmole), ethoxyacetyl chloride (0.74 g, 6.1 mmole) and acetonitrile (100 mL) were combined and stirred at ambient temperature for about 15 minutes to provide a heterogeneous reaction mixture. p-Toluenesulfonic acid (0.1 g) was added and the reaction mixture was heated at reflux for 48 hours. The reaction mixture was cooled to ambient temperature, concentrated under vacuum and then partitioned between methylene chloride and 10% ammonium hydroxide. The organic phase was dried over magnesium sulfate then concentrated to provide 2.8 g of an oil. The oil was dissolved in toluene (100 mL), combined with phosphorus oxychloride (1 mL) and then heated at reflux for 48 hours. The reaction mixture was cooled to ambient temperature, concentrated and then partitioned between methylene chloride and 10% ammonium hydroxide. The organic phase was dried over magnesium sulfate then concentrated to provide a yellow oil. Analysis of the nuclear magnetic resonance spectrum of this material indicated that it contained 2-chloromethyl-6-methyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine and 2-ethoxymethyl-6-methyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine.

Part B

The mixture from Part A was dissolved in methylene chloride (5 mL) then combined with morpholine (2 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution then partitioned between methylene chloride and water. The organic phase was dried over

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magnesium sulfate then concentrated to provide 1.2 g of an oil. This oil was chromatographed (silica gel; 80:20 hexane:ethyl acetate) to provide 0.6 g of 6-methyl-1-(2-methylpropyl)-2-morpholinomethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine and 0.4 g of 2-ethoxymethyl-6-methyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine.

#### Part C

Using the general method of Example 45, 6-methyl-1-(2-methylpropyl)-2-morpholinomethyl-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (0.6 g, Part B) was hydrogenolized to provide 0.31 g of the desired product as a white solid, m.p. 188-190°C. Analysis: Calculated for C<sub>16</sub>H<sub>25</sub>N<sub>5</sub>O + ½H<sub>2</sub>O: %C, 62.11; %H, 8.36; %N, 22.63; Found: %C, 62.19; %H, 8.18; %N, 22.62.

#### Example 60

2-Ethoxymethyl-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine

Using the general method of Example 45, 2-ethoxymethyl-6-methyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine (0.4 g, Example 73, Part B) was hydrogenolized to provide 0.08 g of the desired product as an off white solid, m.p. 72-74°C. Analysis: Calculated for C<sub>14</sub>H<sub>22</sub>N<sub>4</sub>O + ½CH<sub>3</sub>OH: %C, 62.56; %H, 8.69; %N, 20.13; Found: %C, 62.93; %H, 8.37; %N, 19.8.

#### Example 61

2-Butyl-6,7-dimethyl-1-(2-methyl-1-propenyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride  
4-Amino-2-butyl-α,α,6,7-tetramethyl-1H-imidazo[4,5-c]pyridine-1-ethanol (about 200 mg) was combined with concentrated hydrobromic acid (50 mL) and heated at reflux overnight. The reaction mixture was

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concentrated under vacuum. The residue was taken up in methanol then diluted with ether. The resulting precipitate was collected then partitioned between methylene chloride and 10% sodium hydroxide. The organic layer was separated, dried over magnesium sulfate then concentrated to provide an oil. The oil was taken up in methanol then combined with 0.05 mL of concentrated hydrochloric acid followed by dilution with ether. The resulting precipitate was collected, rinsed with ether and dried to provide 60 mg of the desired product as a white solid, m.p. 205°C (dec.). Analysis: Calculated for  $C_{16}H_{24}N_4 + 1.6 HCl$ : %C, 58.10; %H, 7.80; %N, 16.94; Found: %C, 57.95; %H, 7.87; %N, 16.89.

#### Example 62

2-Butyl-7-ethyl-6-methyl-1-(2-methylpropyl)-  
1H-imidazo[4,5-c]pyridin-4-amine Hydrochloride

##### Part A

Using the general method of Example 3, 5-ethyl-4-hydroxy-6-methyl-3-nitro-2(1H)-pyridinone (1.0 g, 5 mmole) was reacted first with trifluoromethanesulfonic anhydride (1.7 mL, 10 mmole) and then with isobutylamine (0.55 mL, 5.5 mmole) to provide 1.0 g of 5-ethyl-6-methyl-4-[(2-methylpropyl)amino]-3-nitro-2-pyridinyl trifluoromethanesulfonate.

##### Part B

Using the general method of Example 10, the material from Part A was reacted with dibenzylamine (0.52 mL) to provide 1.0 g of 5-ethyl-6-methyl-N<sup>4</sup>-(2-methylpropyl)-3-nitro-N<sup>2</sup>,N<sup>2</sup>-bis(phenylmethyl)pyridine-2,4-diamine.

##### Part C

Using the general method of Example 18, the material from Part B was reduced to provide 0.85 g of 5-ethyl-6-methyl-N<sup>4</sup>-(2-methylpropyl)-N<sup>2</sup>,N<sup>2</sup>-

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bis(phenylmethyl)pyridine-2,3,4-triamine as a light brown oil.

#### Part D

The material from Part C was dissolved in acetonitrile (20 mL) then combined with valeryl chloride (0.28 mL) and stirred first at ambient temperature overnight, then at reflux for 3 hours and then at ambient temperature over the weekend. The reaction mixture was concentrated under vacuum. The residue was taken up in methylene chloride, washed with 10% sodium hydroxide, dried over magnesium sulfate then filtered through a layer of silica gel eluting with 30% ethyl acetate in hexane. The filtrate was concentrated under vacuum to provide 0.65 g of 2-butyl-7-ethyl-6-methyl-1-(2-methylpropyl)-N<sup>4</sup>,N<sup>4</sup>-bis(phenylmethyl)-1H-imidazo[4,5-c]pyridin-4-amine as a golden oil.

#### Part E

The material from Part D was dissolved in formic acid (20 mL), combined with palladium hydroxide on carbon (0.5 g, Pearlman's catalyst) then heated at reflux. The reaction mixture was filtered through a layer of celite eluting with methanol to remove the catalyst then concentrated under vacuum. The residue was partitioned between methylene chloride and aqueous sodium bicarbonate. The methylene chloride layer was dried over magnesium sulfate then concentrated under vacuum. The residue was recrystallized from ethyl acetate/hexane to provide product which by nuclear magnetic resonance spectroscopy contained some formate salt. This material was taken up in methanol, combined with 10% sodium hydroxide then heated on a steam bath for 1 hour. The mixture was concentrated to remove the methanol then extracted with methylene chloride. The methylene chloride extract was dried with magnesium sulfate then concentrated under vacuum to provide an oily residue. This residue was taken up in diethyl ether then combined with 1 equivalent of 1 M

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hydrochloric acid in ether. The resulting precipitate was collected by filtration and dried to provide 0.15 g of the desired product as a solid, m.p. 217-219°C. Analysis: Calculated for  $C_{17}H_{28}N_4 \cdot HCl$ : %C, 62.85; %H, 9.00; %N, 17.24; Found: %C, 62.39; %H, 8.70; %N, 16.76.

#### INTERFERON ( $\alpha$ ) INDUCTION IN HUMAN CELLS

An in vitro human blood cell system was used to assess interferon induction by compounds of the invention. Activity is based on the measurement of interferon secreted into culture media. Interferon is measured by bioassay.

##### Blood Cell Preparation for Culture

Whole blood is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBM's) are separated from whole blood by using either LeucoPREP™ Brand Cell Separation Tubes (available from Becton Dickinson) or Ficoll-Paque® solution (available from Pharmacia LKB Biotechnology Inc, Piscataway, NJ). The PBM's are suspended at  $1 \times 10^6$ /mL in RPMI 1640 media (available from GIBCO, Grand Island, NY) containing 25 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and L-glutamine (1% penicillin-streptomycin solution added) with 10% heat inactivated (56°C for 30 minutes) autologous serum added. 200  $\mu$ L portions of PBM suspension are added to 96 well (flat bottom) MicroTest III sterile tissue culture plates.

##### Compound Preparation

The compounds are solubilized in ethanol, dimethyl sulfoxide or tissue culture water then diluted with tissue culture water, 0.01N sodium hydroxide or 0.01N hydrochloric acid (The choice of solvent will depend on the chemical characteristics of the compound being tested.). Ethanol or DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are initially tested in a

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concentration range of from about 0.1  $\mu\text{g/mL}$  to about 5  $\mu\text{g/mL}$ . Compounds which show induction at a concentration of 0.5  $\mu\text{g/mL}$  are then tested in a wider concentration range.

#### Incubation

The solution of test compound is added in a volume (less than or equal to 50  $\mu\text{L}$ ) to the wells containing 200  $\mu\text{L}$  of PBM's in media. Solvent and/or media is added to control wells (wells with no test compound) and as needed to adjust the final volume of each well to 250  $\mu\text{L}$ . The plates are covered with plastic lids, vortexed gently and then incubated for 48 hours at 37°C with a 5% carbon dioxide atmosphere.

#### Separation

Following incubation, the plates are covered with parafilm and then centrifuged at 1000 rpm for 10 to 15 minutes at 4°C in a Damon IEC Model CRU-5000 centrifuge. Media (about 200  $\mu\text{L}$ ) is removed from 4 to 8 wells and pooled into 2 mL sterile freezing vials. Samples are maintained at -70°C until analysis.

#### Interferon Analysis/Calculation

Interferon is determined by bioassay using A549 human lung carcinoma cells challenged with encephalomyocarditis. The details of the bioassay method have been described by G. L. Brennan and L. H. Kronenberg in "Automated Bioassay of Interferons in Micro-test Plates", Biotechniques, June/July; 78, 1983, incorporated herein by reference. Briefly stated the method is as follows: interferon dilutions and A549 cells are incubated at 37°C for 12 to 24 hours. The incubated cells are infected with an inoculum of encephalomyocarditis virus. The infected cells are incubated for an additional period at 37°C before quantifying for viral cytopathic effect. The viral cytopathic effect is quantified by staining followed by spectrophotometric absorbance measurements. Results are expressed as alpha reference units/mL based on the



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value obtained for NIH HU IF-L standard. The interferon was identified as essentially all interferon alpha by testing in checkerboard neutralization assays against rabbit anti-human interferon (beta) and goat anti-human interferon (alpha) using A549 cell monolayers challenged with encephalomyocarditis virus. Results are shown in the table below wherein the absence of an entry indicates that the compound was not tested at that particular concentration.

Interferon ( $\alpha$ ) Induction in Human Cells												
Compound of Example Number	$\alpha$ Reference units/mL											
	Dose Concentration ( $\mu\text{g/mL}$ )											
	0.001	0.005	0.01	0.05	0.1	0.5	1.0	5.0	10	25		
45			0	3	0	1	3	93				
46			4	4	4	4	4	50				
47	8	8	1	190	190	65	61	49				
48			1	1	1	1	1	110	100	19		
49			1	1	10	930	830	70				
50			1	1		1	1	9	37	210		
51			1	1	23	520	520	100				
52	1	82	160	45	150	150	150	320				
53			1	230	780	280	87	70				
54			1	260	880	70	70	70				
55			1	8	130	340	210	110				

Interferon ( $\alpha$ ) Induction in Human Cells												
Compound of Example Number	$\alpha$ Reference units/mL											
	Dose Concentration ( $\mu\text{g/mL}$ )											
	0.001	0.005	0.01	0.05	0.1	0.5	1.0	5.0	10	25		
56			4	680	1100	130	150	200				
57			4	4	4	4	2	320				
58			3	3	7	790	1200	150				
59			1	1	1	1	1	1	1	1		
60			1	1	1	10	230	170	61	61		
61			3	684	395	684	300	520				
62			107	42	62	81	81	81				

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## INDIRECT IN-VITRO ANTIVIRAL ACTIVITY

The test method described below demonstrates the ability of compounds of the invention to inhibit the progress of viral infection.

Whole blood is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBM's) are isolated using Ficoll-Paque® solution (available from Pharmacia LKB Biotechnology Inc., Piscataway, NJ). The PBM's are washed with phosphate buffer saline then diluted with RPMI 1640 medium (available from GIBCO, Grand Island, New York) and 10% fetal bovine serum to obtain a final concentration of  $2.5 \times 10^6$  cells/mL. One mL portions of PBM's in medium are placed in 15 mL polypropylene tubes. The test compound is dissolved in dimethyl sulfoxide then diluted with RPMI 1640 medium. The solution of test compound is added to the tubes containing the PBM's to give final concentrations ranging from 0.1  $\mu$ g/mL to 1.0  $\mu$ g/mL. Control tubes do not receive any test compound. The tubes are then incubated for 24 hours at 37°C with a 5% carbon dioxide atmosphere. Following incubation the tubes are centrifuged at 400 xg for 5 minutes. The supernatant is removed. The PBM's are brought up in 100  $\mu$ L of RPMI 1640 medium and then infected with a 100  $\mu$ L containing  $10^5$  tissue culture 50% infectious doses of vesicular stomatitis virus (VSV). The tubes are incubated for 30 minutes at 37°C to allow virus adsorption. One mL of RPMI 1640 medium is added to each tube and the tubes are incubated for 48 hours at 37°C. The tubes are frozen then thawed to lyse the cells. The tubes are centrifuged at 400 xg for 5 minutes to remove cellular debris then the supernatant is assayed by serial tenfold dilutions on Vero cells in 96 well microtiter plates. The infected cells are incubated for 24 hours at 37°C before quantifying for viral cytopathic effect. The viral cytopathic effect

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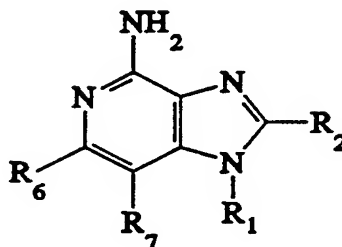
is quantified by staining with 0.05% crystal violet. Results are presented as VSV inhibition, defined as the  $\log_{10}$  (control VSV yield/experimental VSV yield). Control tubes have a value of 0. Results are shown in the table below.

In-vitro Antiviral Activity			
Compound of Example Number	VSV Yield Inhibition		
	Dose Concentration ( $\mu\text{g/mL}$ )		
	0.1	0.5	1.0
45	0.0	0.0	0.0
47	5.0	5.0	6.0
41	0.0	3.0	4.0
50	0.0	0.0	0.0
53	5.0	7.0	6.0
54	4.0	5.0	5.0
56	5.0	5.0	6.0
57	0.0	0.0	2.0
59	0.0	0.0	0.0
60	0.0	2.0	6.0
61	5.0	5.0	6.0

The claimed invention is:

1. A compound of the formula

5



- 10 wherein R<sub>1</sub> is selected from the group consisting of  
hydrogen; CHR<sub>x</sub>R<sub>y</sub> wherein R<sub>x</sub> is hydrogen and R<sub>y</sub> is  
selected from the group consisting of straight chain,  
branched chain, or cyclic alkyl containing one to about  
ten carbon atoms, straight chain or branched chain  
15 alkenyl containing two to about ten carbon atoms,  
straight chain or branched chain hydroxyalkyl  
containing one to about six carbon atoms, alkoxyalkyl  
wherein the alkoxy moiety contains one to about four  
carbon atoms and the alkyl moiety contains one to about  
20 six carbon atoms, and phenylethyl; and -CH=CR<sub>z</sub>R<sub>z</sub> wherein  
each R<sub>z</sub> is independently straight chain, branched chain,  
or cyclic alkyl of one to about six carbon atoms;

- R<sub>2</sub> is selected from the group consisting of  
hydrogen, straight chain or branched chain alkyl  
25 containing one to about eight carbon atoms, straight  
chain or branched chain hydroxyalkyl containing one to  
about six carbon atoms, alkoxyalkyl wherein the alkoxy  
moiety contains one to about four carbon atoms and the  
alkyl moiety contains one to about six carbon atoms,  
30 benzyl, (phenyl)ethyl and phenyl, the benzyl,  
(phenyl)ethyl or phenyl substituent being optionally  
substituted on the benzene ring by a moiety selected  
from the group consisting of methyl, methoxy, and

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halogen; and morpholinoalkyl wherein the alkyl moiety contains one to about four carbon atoms;

$R_6$  and  $R_7$  are independently selected from the group consisting of hydrogen and alkyl of one to about five  
5 carbon atoms,

with the proviso that  $R_6$  and  $R_7$  taken together contain no more than six carbon atoms, and with the further proviso that when  $R_7$  is hydrogen then  $R_6$  is other than hydrogen and  $R_2$  is other than hydrogen or  
10 morpholinoalkyl, and with the further proviso that when  $R_6$  is hydrogen then  $R_7$  and  $R_2$  are other than hydrogen.

2. A compound according to Claim 1, wherein  $R_1$  substituents is selected from the group consisting of  
15 2-methylpropyl, n-butyl, 2-methyl-1-propenyl, ethoxyethyl, 2-hydroxy-2-methylpropyl, and 2-phenylethyl.

3. A compound according to Claim 1, wherein  $R_2$  is  
20 methyl, ethyl, propyl, or butyl.

4. A compound according to Claim 1, wherein  $R_2$  hydroxymethyl.

25 5. A compound according to Claim 1, wherein  $R_2$  is ethoxymethyl.

6. A compound according to Claim 1, wherein  $R_6$  and  $R_7$  are independently selected from the group consisting  
30 of alkyl of one to about four carbon atoms.

7. A compound according to Claim 1, wherein  $R_6$  and  $R_7$  are methyl.

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8. A compound according to Claim 2, wherein R<sub>2</sub> is methyl, ethyl, propyl, butyl, hydroxymethyl, or ethoxymethyl.

- 5           9. A compound according to Claim 1, selected from the group consisting of: 2,7-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          2,6,7-trimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
10          4-amino- $\alpha,\alpha$ ,2,6,7-pentamethyl-1H-imidazo[4,5-c]pyridine-1-ethanol;  
          4-amino-2-butyl- $\alpha,\alpha$ ,6,7-tetramethyl-1H-imidazo[4,5-c]pyridine-1-ethanol;  
          4-amino-2-ethoxymethyl- $\alpha,\alpha$ ,6,7-tetramethyl-1H-  
15 imidazo[4,5-c]pyridine-1-ethanol;  
          1-(2-ethoxyethyl)-2,7-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine;  
          2-butyl-7-ethyl-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride;  
20          2,6-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          2-ethyl-6,7-dimethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          2,6,7-trimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-  
25 c]pyridin-4-amine;  
          2-butyl-6,7-dimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          6,7-dimethyl-1-(2-phenylethyl)-2-phenylmethyl-1H-imidazo[4,5-c]pyridin-4-amine;  
30          2,6-dimethyl-1-(2-phenylethyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          2-ethoxymethyl-6-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]pyridin-4-amine;  
          4-amino-6-methyl-1-(2-methylpropyl)-1H-  
35 imidazo[4,5-c]pyridine-2-methanol;  
          1-butyl-2,6-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine; and



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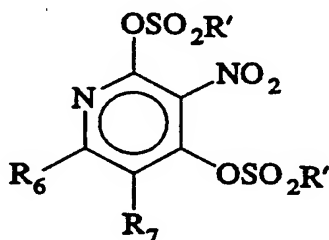
2-butyl-6,7-dimethyl-1-(2-methyl-1-propenyl)-1H-imidazo[4,5-c]pyridin-4-amine hydrochloride.

10. A method of treating a viral infection in an animal comprising the step of administering to said animal a compound according to Claim 1 in an amount effective to inhibit the viral infection.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable vehicle.

12. A method of inducing interferon biosynthesis in an animal, comprising the step of administering to said animal a compound according to Claim 1 in an amount effective to induce said interferon biosynthesis.

13. A compound of the formula

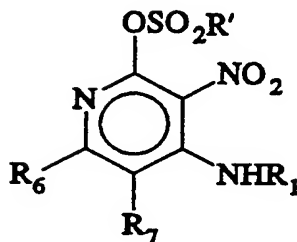


wherein R<sub>6</sub> and R<sub>7</sub> are independently selected from the group consisting of hydrogen and alkyl of one to about five carbon atoms, with the proviso that R<sub>6</sub> and R<sub>7</sub> taken together contain no more than six carbon atoms, and with the further proviso that when R<sub>7</sub> is hydrogen then R<sub>6</sub> is other than hydrogen; and R' is alkyl, perfluoroalkyl, alkylaryl, or haloaryl.

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14. A compound of the formula

5



10 wherein R<sub>1</sub> is selected from the group consisting of  
hydrogen; CHR<sub>x</sub>R<sub>y</sub> wherein R<sub>x</sub> is hydrogen and R<sub>y</sub> is  
selected from the group consisting of straight chain,  
branched chain, or cyclic alkyl containing one to about  
ten carbon atoms, straight chain or branched chain  
15 alkenyl containing two to about ten carbon atoms,  
straight chain or branched chain hydroxyalkyl  
containing one to about six carbon atoms, alkoxyalkyl  
wherein the alkoxy moiety contains one to about four  
carbon atoms and the alkyl moiety contains one to about  
20 six carbon atoms, and phenylethyl; and -CH=CR<sub>2</sub>R<sub>3</sub> wherein  
each R<sub>2</sub> is independently straight chain, branched chain,  
or cyclic alkyl of one to about six carbon atoms;

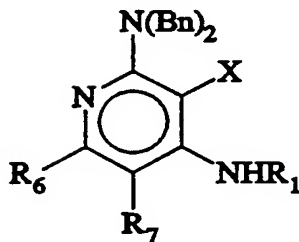
R<sub>6</sub> and R<sub>7</sub> are independently selected from the group  
consisting of hydrogen and alkyl of one to about five  
25 carbon atoms, with the proviso that R<sub>6</sub> and R<sub>7</sub> taken  
together contain no more than six carbon atoms, and  
with the further proviso that when R<sub>7</sub> is hydrogen then  
R<sub>6</sub> is other than hydrogen; and

R' is alkyl, perfluoroalkyl, alkylaryl, or  
30 haloaryl.

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15. A compound of the formula

5

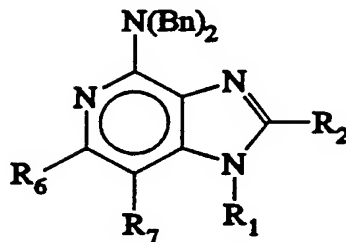
10 wherein  $X$  is  $-NO_2$  or  $-NH_2$ ;

$R_6$  and  $R_7$  are independently selected from the group consisting of hydrogen and alkyl of one to about five carbon atoms, with the proviso that  $R_6$  and  $R_7$  taken together contain no more than six carbon atoms, and  
15 with the further proviso that when  $R_7$  is hydrogen then  $R_6$  is other than hydrogen;

$R_1$  is selected from the group consisting of hydrogen;  $CHR_xR_y$ , wherein  $R_x$  is hydrogen and  $R_y$  is selected from the group consisting of straight chain,  
20 branched chain, or cyclic alkyl containing one to about ten carbon atoms, straight chain or branched chain alkenyl containing two to about ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to about six carbon atoms, alkoxyalkyl  
25 wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms, and phenylethyl; and  $-CH=CR_zR_z$ , wherein each  $R_z$  is independently straight chain, branched chain, or cyclic alkyl of one to about six carbon atoms; and  
30 Bn is a hydrogenolizable amino substituent.

16. A compound of the formula

5



10        wherein  $R_1$  is selected from the group consisting of  
hydrogen;  $\text{CHR}_x\text{R}_y$  wherein  $R_x$  is hydrogen and  $R_y$  is  
selected from the group consisting of straight chain,  
branched chain, or cyclic alkyl containing one to about  
ten carbon atoms, straight chain or branched chain  
15 alkenyl containing two to about ten carbon atoms,  
straight chain or branched chain hydroxyalkyl  
containing one to about six carbon atoms, alkoxyalkyl  
wherein the alkoxy moiety contains one to about four  
carbon atoms and the alkyl moiety contains one to about  
20 six carbon atoms, and phenylethyl; and  $-\text{CH}=\text{CR}_z\text{R}_2$  wherein  
each  $R_z$  is independently straight chain, branched chain,  
or cyclic alkyl of one to about six carbon atoms;

$R_2$  is selected from the group consisting of  
hydrogen, straight chain or branched chain alkyl  
25 containing one to about eight carbon atoms, straight  
chain or branched chain hydroxyalkyl containing one to  
about six carbon atoms, alkoxyalkyl wherein the alkoxy  
moiety contains one to about four carbon atoms and the  
alkyl moiety contains one to about six carbon atoms,  
30 benzyl, (phenyl)ethyl and phenyl, the benzyl,  
(phenyl)ethyl or phenyl substituent being optionally  
substituted on the benzene ring by a moiety selected  
from the group consisting of methyl, methoxy, and  
halogen; and morpholinoalkyl wherein the alkyl moiety  
35 contains one to about four carbon atoms;

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$R_6$  and  $R_7$  are independently selected from the group consisting of hydrogen and alkyl of one to about five carbon atoms, with the proviso that  $R_6$  and  $R_7$  taken together contain no more than six carbon atoms, and  
5 with the further proviso that when  $R_7$  is hydrogen then  $R_6$  is other than hydrogen and  $R_2$  is other than hydrogen or morpholinoalkyl, and with the further proviso that when  $R_6$  is hydrogen then  $R_7$  and  $R_2$  are other than hydrogen; and  
10 Bn is a hydrogenolizable amino substituent.

## INTERNATIONAL SEARCH REPORT

Int onal Application No  
PCT/US 94/06891

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D471/04 A61K31/435 C07D213/69 C07D213/74 C07D213/75  
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 510 260 (TOYO JOZO) 28 October 1992 cited in the application see claims 1,7	1,9
X	--- RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol.80, 1961, DEN HAAG NL pages 545 - 555 C.A. SALEMINK 'Über 2-Propyl-1- und 3-Desazaadenin' see page 552, compound IX --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

28 September 1994

Date of mailing of the international search report

12. 10. 94

Name and mailing address of the ISA

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Fax: (+ 31-70) 340-3016

Authorized officer

Alfaro Faus, I

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/06891

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 61, no. 1, 1964, Columbus, Ohio, US; D.H. BRANTS ET AL. 'The distribution of tobacco mosaic virus (TMV) in excised tomato roots cultivated in vitro' column 6060G ; see anbstract, compound 1 &amp; TIJDSCHR. PLANTENZIEKTEN 68, 198-207 (1962)</p> <p>-----</p>	1

# INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 94/ 06891

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 10 and 12 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ ~~As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.~~
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



### Information on patent family members

PCT/US 94/06891

Form PCT/ISA/210 (patent family annex) (July 1992)



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 471/04, 403/10, 405/14, 409/14, 413/14, 417/14, 487/04, A61K 31/435, 31/50</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/16687</b> <b>(43) International Publication Date:</b> 22 June 1995 (22.06.95)
<b>(21) International Application Number:</b> PCT/US94/14112 <b>(22) International Filing Date:</b> 8 December 1994 (08.12.94)  <b>(30) Priority Data:</b> 08/168,564           16 December 1993 (16.12.93)   US 08/324,631           18 October 1994 (18.10.94)   US 08/347,528           5 December 1994 (05.12.94)   US  <b>(71) Applicant:</b> ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).  <b>(72) Inventors:</b> SUMMERS, James, B., Jr.; 1955 St. Andrews Drive, Libertyville, IL 60048 (US). DAVIDSEN, Steven, K.; 1002 Gracewood, Libertyville, IL 60048 (US). CURTIN, Michael, L.; 2205 Rolling Ridge Lane, Linden- hurst, IL 60046 (US). HEYMAN, H., Robin; 400 North McClurg Court, Chicago, IL 60610 (US). SHEPPARD, George, S.; 300 Laurel Avenue, Wilmette, IL 60091 (US). XU, Lianhong; 219 Adler Drive, Libertyville, IL 60048 (US). CARRERA, George, M., Jr.; 9379 Bay Colony Drive, Des Plaines, IL 60016 (US). GARLAND, Robert, B.; 2529 Walters Avenue, Northbrook, IL 60062 (US).		<b>(74) Agents:</b> JANSSEN, Jerry, F. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).  <b>(81) Designated States:</b> AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). -  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PLATELET ACTIVATING FACTOR ANTAGONISTS: IMIDAZOPYRIDINE INDOLES  <div style="text-align: center; margin: 20px 0;"> </div> <div style="text-align: right; margin-top: -20px;"> <b>(I)</b> </div> <b>(57) Abstract</b> <p>The present invention relates to compounds of formula (I) and the pharmaceutically acceptable salts thereof which are potent antagonists of PAF and are useful in the treatment of PAF-related disorders including asthma, shock, respiratory distress syndrome, acute inflammation, transplanted organ rejection, gastrointestinal ulceration, allergic skin diseases, delayed cellular immunity, parturition, fetal lung maturation, and cellular differentiation.</p>		

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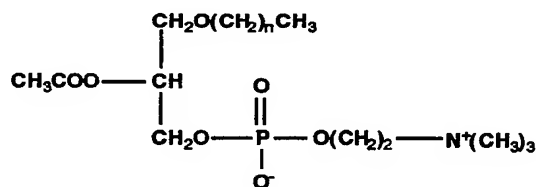
# PLATELET ACTIVATING FACTOR ANTAGONISTS: IMIDAZOPYRIDINE INDOLES

## Technical Field

5 This invention relates to compounds having pharmacological activity, to compositions containing these compounds, and to a medical method of treatment employing the compounds and compositions. More particularly, this invention concerns certain indolecarbonyl pyridylpyrrolothiazole compounds and their salts which have platelet activating factor (PAF) antagonist activity, to pharmaceutical  
10 compositions containing these compounds, and to a method of treating PAF-mediated disorders.

## Background of the Invention

Platelet activating factor (PAF) is a phospholipid released from human and  
15 other animal cells and is an acetylglyceryl ether of phosphorylcholine as represented by the following formula:



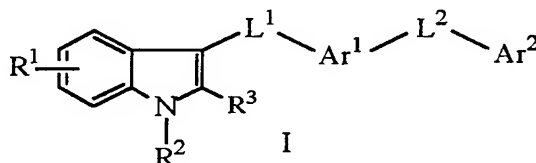
20 where n is 15 or 17.

PAF is physiologically active and causes contraction of the airway smooth muscle, increased vascular permeability, platelet aggregation, hypotension, and the like. It is now recognized as a powerful mediator of inflammation and may play a physiological or pathobiological role in a variety of clinical conditions, such as asthma  
25 and pulmonary dysfunction, acute inflammation, transplanted organ rejection, shock, thrombosis, anaphylaxis, gastrointestinal ulceration, allergic skin diseases, retinal and corneal diseases, chemically induced liver cirrhosis, and ovimplantation in pregnancy. Accordingly, compounds possessing PAF antagonistic effects should be of value in the treatment of any of the above conditions.

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Summary of the Invention

The present invention provides, in its principal aspect, compounds having PAF antagonist activity of formula I:



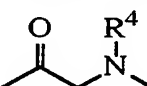
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or the pharmaceutically acceptable salt thereof where **R<sup>1</sup>** is one or more groups independently selected from the group consisting of (a) hydrogen, (b) halogen, (c) hydroxy, (d) cyano, (e) alkyl of one to six carbon atoms, (f) alkynyl of two to four carbon atoms, (g) alkoxy of one to six carbon atoms, (h) alkanoyl of one to seven carbon atoms, (i) -COOR<sup>6</sup>, where R<sup>6</sup> is hydrogen, alkyl of one to ten carbon atoms, or phenylalkyl where the alkyl portion is of one to four carbon atom, (j) phenyl, optionally substituted with (j-1) alkyl of one to six carbon atoms, (j-2) alkoxy of one to six carbon atoms, (j-3) halogen, (j-4) -NR<sup>4</sup>R<sup>5</sup>, where R<sup>4</sup> and R<sup>5</sup> are independently selected from hydrogen and alkyl of one to six carbon atoms, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring, (j-5) -COOR<sup>6</sup>, (j-6) -CONR<sup>4</sup>R<sup>5</sup>, or (j-7) -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, (k) -C(O)NR<sup>4</sup>R<sup>5</sup>, (l) -OC(O)NR<sup>4</sup>R<sup>5</sup>, (m) -NHC(O)NR<sup>4</sup>R<sup>5</sup>, (n) 2- or 3-furyl, (o) 2- or 3-thienyl, (p) 2-, 4-, or 5-thiazolyl, (q) 2-, 3-, or 4-pyridyl, (r) 2-, or 4-pyrimidyl, (s) phenylalkyl, in which the alkyl portion contains one to six carbon atoms and the phenyl moiety is optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (t) benzoyl, optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (u) phenoxy, optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (v) phenylalkyloxy, in which the alkyl portion contains from one to six carbon atoms and the phenyl moiety is optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, and (w) phenylalkanoyl, in which the alkanoyl portion contains one to seven carbon atoms and the phenyl moiety is optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of from one to six carbon atoms.

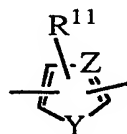
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$R^2$  is selected from the group consisting of (a) hydrogen, (b) alkyl of one to six carbon atoms, (c)  $-(CH_2)_pCOOR^6$ , where  $p$  is 0, 1, 2, 3, or 4, (d)  $-(CH_2)_qNR^4R^5$ , where  $q$  is 2, 3, or 4, (e)  $-(CH_2)_pCOR^6$ , (f)  $-(CH_2)_qOR^6$ , (g)  $-(CH_2)_pSO_2R^6$ , (h)  $-(CH_2)_pSO_2NR^4R^5$ , (i)  $-(CH_2)_pCONR^7R^8$ , where  $R^7$  and  $R^8$  are independently selected from (i-1) hydrogen, (i-2) alkyl of one to six carbon atoms, (i-3)  $-(CH_2)_rCOOR^6$ , where  $r$  is 1, 2, 3, or 4, (i-4)  $-(CH_2)_rNR^4R^5$ , (i-5)  $-(CH_2)_rOH$ , (i-6)  $-(CH_2)_rSO_2R^6$ , and (i-7)  $-(CH_2)_rSO_2NR^4R^5$ , (j)  $-(CH_2)_pCN$ , (k)  $-(CH_2)_p-1H$ -tetrazol-5-yl, (l)  $-CONHNH_2$ , and (m) phenylalkyl wherein the alkyl portion is of one to four carbon atoms, and the phenyl moiety is optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of from one to six carbon atoms, or  $R^7$  and  $R$ , taken together with the nitrogen atom to which they are attached, for a pyrrolidinyl or morpholinyl ring.

$R^3$  is selected from the group consisting of hydrogen and alkyl of from one to six carbon atoms, and  $L^1$  is selected from the group consisting of

(a)  $>C=O$ , (b) , (c)  $>C=NNR^9R^{10}$ , where  $R^9$ , and  $R^{10}$  are independently selected from hydrogen, alkyl of one to six carbon atoms, alkoxy carbonyl of two to six carbon atoms, aminocarbonyl, alkylaminocarbonyl of two to six carbon atoms, dialkylaminocarbonyl in which the alkyl groups are independently of one to six carbon atoms, alkanoyl of one to six carbon atoms, and phenyl, optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of from one to six carbon atoms, (d)  $>C=NOR^9$ , (e)  $>S(O)_n$ , where  $n$  is 1 or 2, and (f)  $-NHSO_2-$ .

$Ar^1$  is a valence bond or a radical of formula



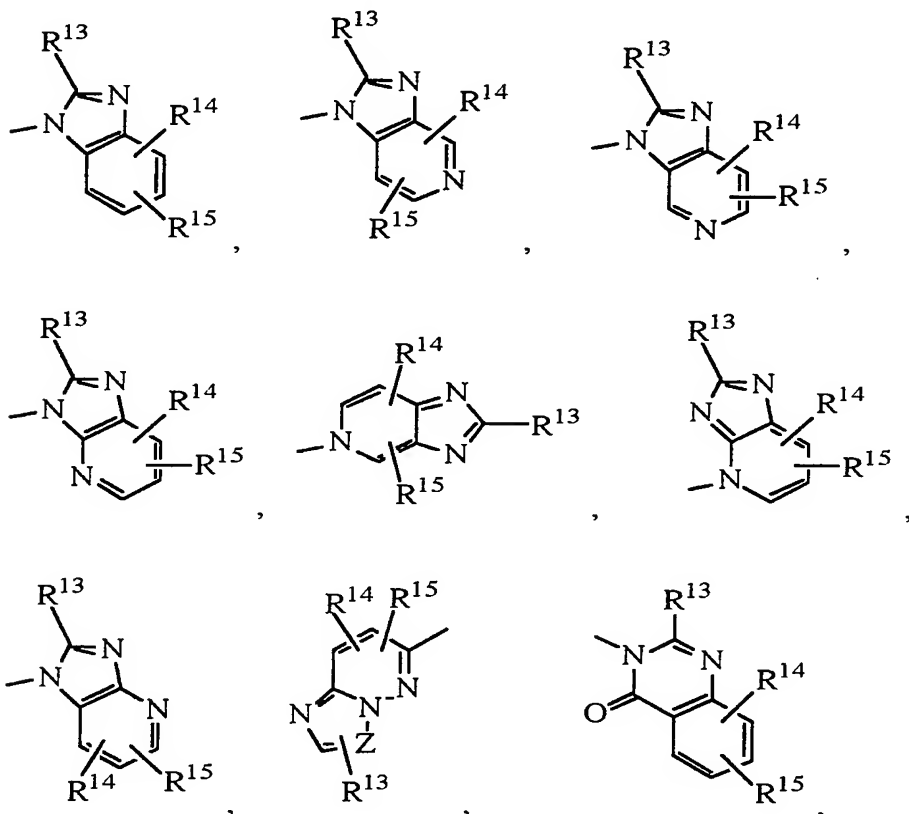
where  $Y$  is O, S, or  $-CH=CH-$ ,  $Z$  is N or CH, and  $R^{11}$  is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, alkenyl of two to six carbon atoms, alkoxy of one to six carbon atoms, and halogen.

$L^2$  is a valence bond or straight-chain alkylene of one to six carbon atoms, optionally substituted with one or more groups selected from (a) alkyl of one to six carbon atoms, (b) alkenyl of two to six carbon atoms, (c) alkoxy carbonyl of one to six carbon atoms, (d) alkoxy of one to six carbon atoms, (e) alkylthio of one to six carbon

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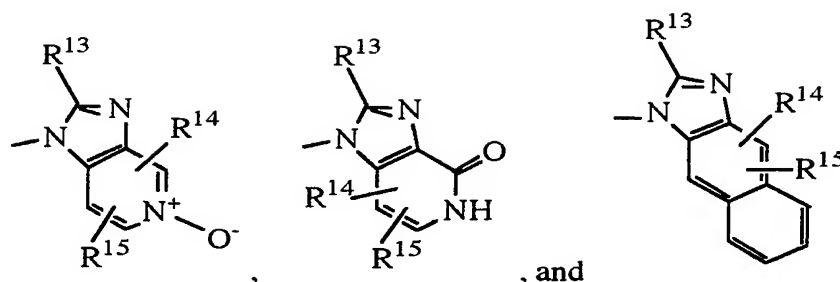
- atoms, (f) alkoxyalkyl in which the alkoxy and alkyl portions are independently one to six carbon atoms, (g) alkylthioalkyl in which the alkyl portions are independently one to six carbon atoms, (h) phenylalkyl wherein the alkyl portion is one to six carbon atoms and where the phenyl ring is optionally substituted with alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, hydroxy, or halogen, and (i) thiophenyl where the phenyl ring is optionally substituted with alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, hydroxy, or halogen, provided that  $L^2$  is optionally substituted alkyl when  $Ar^1$  is a valence bond.

10  $Ar^2$  is selected from the group consisting of



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where Z is defined above, and R<sup>13</sup> is selected from the group consisting of (a) alkyl of one to six carbon atoms, (b) alkenyl of two to six carbon atoms, (c) alkoxy of one to six carbon atoms, (d) alkylthio of one to six carbon atoms, (e) alkoxyalkyl in which the alkoxy and alkyl portions are independently one to six carbon atoms, (f) alkylthioalkyl in which the alkyl portions are independently one to six carbon atoms, (g) haloalkyl, (h) phenylalkyl wherein the alkyl portion is of one to six carbon atoms and the phenyl ring is optionally substituted with alkyl of one to six carbon atoms, (i) cycloalkyl of three to eight carbon atoms, and (j) thiophenyl where the phenyl ring is optionally substituted with alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, hydroxy, or halogen. R<sup>14</sup> and R<sup>15</sup> are independently selected from the group consisting of (a) hydrogen, (b) alkyl of one to six carbon atoms, (c) alkenyl of two to six carbon atoms, (d) halogen, (e) cyano, (f) carboxyl, (g) alkoxycarbonyl of from two to six carbon atoms, (h) aminocarbonyl, (i) alkylaminocarbonyl of one to six carbon atoms, (j) dialkylaminocarbonyl in which the alkyl groups are independently one to six carbon atoms, (k) alkanoyl, (l) hydroxyalkyl, (m) haloalkyl, (n) alkoxy of one to six carbon atoms, (o) alkylthio of one to six carbon atoms, (p) alkylsulfinyl of one to six carbon atoms, (q) alkylsulfonyl of one to six carbon atoms, (r) amino, (s) alkonylamino, and (t) nitro, or R<sup>14</sup> and R<sup>15</sup>, together with the carbon atoms to which they are attached define a phenyl ring or 5- to 7-membered cycloalkylene ring.

Compounds of the present invention may exhibit stereoisomerism by virtue of the presence of one or more asymmetric or chiral centers in the compounds. The present invention contemplates the various stereoisomers and mixtures thereof. Desired enantiomers are obtained by chiral synthesis from commercially available chiral starting materials by methods well known in the art, or may be obtained from mixtures of the enantiomers by resolution using known techniques.



In another aspect, the present invention provides pharmaceutical compositions useful for the treatment of PAF-mediated disorders comprising a therapeutically effective amount of a compound of formula I above in combination with a pharmaceutically acceptable carrier.

5 In another aspect, the present invention provides a method of inhibiting PAF activity by administering to a host mammal in need of such treatment an effective amount of a PAF-inhibiting compound having structure I above.

In yet another aspect of the present invention, there is provided a method of treating PAF-mediated disorders including asthma, shock, respiratory distress  
10 syndrome, acute inflammation, delayed cellular immunity, parturition, fetal lung maturation, and cellular differentiation by administering to a host mammal in need of such treatment a therapeutically effective amount of a compound of structure I above.

#### Detailed Description of the Invention

##### 15 Definitions of Terms

As used throughout this specification and the appended claims, the following terms have the meanings specified.

The term "alkyl" refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single hydrogen atom.

20 Alkyl groups are exemplified by methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and the like.

The term "alkylamino" refers to a group having the structure -NHR' wherein R' is alkyl, as previously defined. Examples of alkylamino include methylamino, ethylamino, *iso*-propylamino and the like.

25 The term "alkylaminocarbonyl" refers to an alkylamino group, as previously defined, attached to the parent molecular moiety through a carbonyl group. Examples of alkylaminocarbonyl include methylamino-carbonyl, ethylaminocarbonyl, *iso*-propylaminocarbonyl and the like.

30 The term "alkylthio" refers to an alkyl group, as defined above, attached to the parent molecular moiety through a sulfur atom and includes such examples as methylthio, ethylthio, propylthio, *n*-, *sec*- and *tert*-butylthio and the like.

The term "alkanoyl" represents an alkyl group, as defined above, attached to the parent molecular moiety through a carbonyl group. Alkanoyl groups are exemplified by formyl, acetyl, propionyl, butanoyl and the like.

The term "alkanoylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of alkanoylamino include formamido, acetamido, and the like.

5 The term "N-alkanoyl-N-alkylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through an aminoalkyl group. Examples of N-alkanoyl-N-alkylamino include N-methylformamido, N-methyl-acetamido, and the like.

10 The terms "alkoxy" or "alkoxyl" denote an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Representative alkoxy groups include methoxyl, ethoxyl, propoxyl, butoxyl, and the like.

The term "alkoxyalkoxyl" refers to an alkyl group, as defined above, attached through an oxygen to an alkyl group, as defined above, attached in turn through an oxygen to the parent molecular moiety. Examples of alkoxyalkoxyl include methoxymethoxyl, methoxyethoxyl, ethoxyethoxyl and the like.

15 The term "alkoxyalkyl" refers to an alkoxy group, as defined above, attached through an alkylene group to the parent molecular moiety.

The term "alkoxycarbonyl" represents an ester group; i.e. an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

20 The term "alkenyl" denotes a monovalent group derived from a hydrocarbon containing at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl and the like.

25 The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like.

30 The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Examples of alkenylene include  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{CH}_3)=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ , and the like.

35 The term "alkynylene" refers to a divalent group derived by the removal of two hydrogen atoms from a straight or branched chain acyclic hydrocarbon group containing a carbon-carbon triple bond. Examples of alkynylene include  $-\text{CH}\equiv\text{CH}-$ ,  $-\text{CH}\equiv\text{CH}-\text{CH}_2-$ ,  $-\text{CH}\equiv\text{CH}-\text{CH}(\text{CH}_3)-$ , and the like.

The term "aryl" is used herein to mean substituted and unsubstituted aromatic carbocyclic radicals and substituted and unsubstituted heterocyclic aromatic radicals including, but not limited to, phenyl, 1-naphthyl or 2-naphthyl, fluorenyl, pyridyl, quinolyl, thienyl, thiazolyl, pyrimidyl, indolyl, and the like.

5       The term "heterocyclic aromatic" is used herein to refer to 5- and 6-membered aromatic rings having in the ring one, two, or three heteroatoms selected from N, O, and S, and also including benzo fused analogs of these 5- and 6-membered heterocyclic aromatic rings including, but not limited to pyridyl, quinolyl, furyl, benzofuryl, thienyl, thiazolyl, pyrimidyl, indolyl, and the like.

10       The term "cycloalkyl" denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, and bicyclo[2.2.2]octanyl.

15       The term "cycloalkylene" refers to a divalent group derived from a saturated carbocyclic hydrocarbon by the removal of two hydrogen atoms, for example cyclopentylene, cyclohexylene, and the like.

20       The term "carbocyclic aryl" denotes a monovalent carbocyclic ring group derived by the removal of a single hydrogen atom from a monocyclic or bicyclic fused or non-fused ring system obeying the " $4n + 2$  p electron" or Huckel aromaticity rule. Examples of carbocyclic aryl groups include phenyl, 1- and 2-naphthyl, biphenyl, fluorenyl, and the like.

25       The term "(carbocyclic aryl)alkyl" refers to a carbocyclic aryl ring group as defined above, attached to the parent molecular moiety through an alkylene group. Representative (carbocyclic aryl)alkyl groups include phenylmethyl, phenylethyl, phenylpropyl, 1-naphthylmethyl, and the like.

30       The term "carbocyclic aryloxyalkyl" refers to a carbocyclic aryl group, as defined above, attached to the parent molecular moiety through an oxygen atom and thence through an alkylene group. Such groups are exemplified by phenoxymethyl, 1- and 2-naphthyloxymethyl, phenoxyethyl and the like.

35       The term "(carbocyclic aryl)alkoxyalkyl" denotes a carbocyclic aryl group as defined above, attached to the parent molecular moiety through an alkoxyalkyl group. Representative (carbocyclic aryl)alkoxyalkyl groups include phenylmethoxymethyl, phenylethoxymethyl, 1- and 2-naphthylmethoxyethyl, and the like.

      "Carbocyclic arylthioalkyl" represents a carbocyclic aryl group as defined above, attached to the parent molecular moiety through a sulfur atom and thence

through an alkylene group and are typified by phenylthiomethyl, 1- and 2-naphthylthioethyl and the like.

The term "dialkylamino" refers to a group having the structure -NR'R" wherein R' and R" are independently selected from alkyl, as previously defined. Additionally, R' and R" taken together may optionally be -(CH<sub>2</sub>)<sub>kk</sub>- where kk is an integer of from 2 to 6. Examples of dialkylamino include, dimethylamino, diethylaminocarbonyl, methylethylamino, piperidino, and the like.

The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

The term "hydroxyalkyl" represents an alkyl group, as defined above, substituted by one to three hydroxyl groups with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group.

The term "phenoxy" refers to a phenyl group attached to the parent molecular moiety through an oxygen atom.

The term "phenylthio" refers to a phenyl group attached to the parent molecular moiety through a sulfur atom.

The term "pyridyloxy" refers to a pyridyl group attached to the parent molecular moiety through an oxygen atom.

The term "metabolically cleavable group" denotes a group which is cleaved *in vivo* to yield the parent molecule of the structural formulae indicated above wherein M is hydrogen. Examples of metabolically cleavable groups include -COR, -COOR, -CONRR and -CH<sub>2</sub>OR radicals where R is selected independently at each occurrence from alkyl, trialkylsilyl, carbocyclic aryl or carbocyclic aryl substituted with one or more of C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy. Specific examples of representative metabolically cleavable groups include acetyl, methoxycarbonyl, benzoyl, methoxymethyl and trimethylsilyl groups.

By "pharmaceutically acceptable salt" it is meant those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1-19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate,

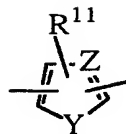
alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-  
5 hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or  
10 alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

15 The terms "PAF-related disorders" and "PAF-mediated disorders" are used herein to mean disorders related to PAF or mediated by PAF, including asthma, shock, respiratory distress syndromes, acute inflammation, gastric ulceration, transplant organ rejection, psoriasis, allergic skin disease, ischemia and reperfusion injury, delayed cellular immunity, parturition, fetal lung maturation, and cellular  
20 differentiation.

#### Preferred Embodiments

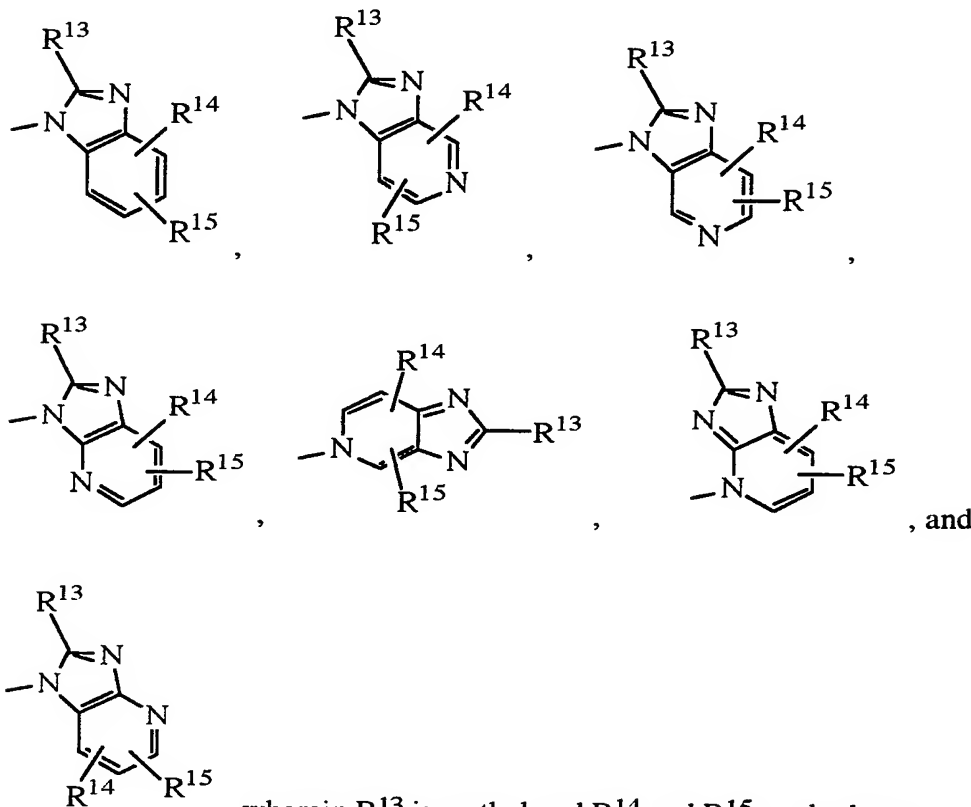
In one preferred embodiment, the compounds of this invention are represented by formula I wherein  $R^3$  is hydrogen;  $L^1$  is  $>C=O$  or  $-SO_2-$ ;  $R^1$  is one or more  
25 groups independently selected from the group consisting of (a) hydrogen, (b) halogen, (c) alkyl of one to six carbon atoms, (d) alkynyl of two to four carbon atoms, (e) alkoxy of one to six carbon atoms, (f)  $-COOR^6$  where  $R^6$  is hydrogen or alkyl of one to six carbon atoms, (g) phenyl, optionally substituted with alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or halogen, (h) phenylalkyl where the alkyl  
30 portion contains one to six carbon atoms and the phenyl moiety is optionally substituted with alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or halogen, (i) phenoxy optionally substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, and (j)  $-OC(O)NR^4R^5$ ;  $L^2$  is a valence bond or methylene;

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Ar<sup>1</sup> is

wherein Y is O, S, or -CH=CH-, Z is N or CH, and R<sup>11</sup>; and Ar<sup>2</sup> is selected from the group consisting of

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, wherein R<sup>13</sup> is methyl and R<sup>14</sup> and R<sup>15</sup> are hydrogen.

In another preferred embodiment, the compounds of this invention are represented by formula I wherein Ar<sup>1</sup> is a valence bond and L<sup>2</sup> is straight-chain alkylene of one to six carbon atoms.

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In another preferred embodiment, the compounds of this invention are represented by formula I wherein R<sup>1</sup> is hydrogen, -COOR<sup>6</sup> where R<sup>6</sup> is hydrogen or alkyl of one to six carbon atoms, 4-fluorophenyl, phenylmethyl, or 4-fluorophenoxy; R<sup>2</sup> is *N,N*-dimethylcarbamoyl or 2-ethoxyethyl; L<sup>1</sup> is >C=O or -SO<sub>2</sub>-; Ar<sup>1</sup> is a valence bond, and L<sup>2</sup> is straight-chain alkylene of one to six carbon atoms.

In the most preferred embodiment the compounds of this invention are represented by formula I wherein **R<sup>1</sup>** is selected from the group consisting of hydrogen, -COOR<sup>6</sup> where R<sup>6</sup> is hydrogen or alkyl of one to six carbon atoms, alkynyl of two to four carbon atoms, 4-fluorophenyl, phenylmethyl, or 4-fluorophenoxy; **R<sup>2</sup>** is *N,N*-dimethylcarbamoyl or 2-ethoxyethyl; **L<sup>1</sup>** is >C=O or -SO<sub>2</sub>-; **Ar<sup>1</sup>** is phenyl or phenyl substituted with alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or halogen, **L<sup>2</sup>** is methylene; and **R<sup>3</sup>** and **Ar<sup>2</sup>** are defined immediately above.

Compounds contemplated as falling within the scope of this invention include, but are not limited to:

- 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole,
- 6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole hydrochloride,
- 6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,
- 6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4.5-c]pyridyl)benzoyl]indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4.5-c]pyrid-1-yl)benzoyl]indole,
- 6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,
- 3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,

- 3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,  
3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
5 1-*N,N*-dimethylcarbamoyl-3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
3-{3-[(3H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{3-[(3H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
10 3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole,  
15 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole,  
20 1-*N,N*-dimethylcarbamoyl-3-{4-[(3H-2-methylimidazo[4.5-b]pyrid-3-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-b]pyrid-1-yl)methyl]benzoyl}indole,  
25 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-trifluoromethylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-(2-propyl)imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
30 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-phenylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-ethylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
35 3-{3-[(5H-2-methylimidazo[4.5-c]pyrid-5-yl)methyl]benzoyl}indole,



- 1-*N,N*-dimethylcarbamoyl-3-{3-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl]benzoyl}indole,
- 1-*p*-toluenesulfonyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyridyl)methyl]benzoyl}indole,
- 5 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)pent-5-ylcarbonyl]indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)pent-5-ylcarbonyl]indole,
- 10 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)pent-5-ylcarbonyl]indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 15 1-*N,N*-dimethylcarbamoyl-5-phenylmethoxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(pyrid-3-yl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 20 1-*N,N*-dimethylcarbamoyl-6-bromo-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 25 1-*N,N*-dimethylcarbamoyl-5-methoxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyloxime}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoylhydrazone}indole,
- 30 1-methyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*tert*-butyloxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 35 1-methoxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,

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- 1-phenoxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-carbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
5 1-*N*-methylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N*-phenyl-*N*-methylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(*N*-methyl-*N*-(dimethylaminoethyl))carbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
10 1-*N*-(2-hydroxyethyl)carbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-hydrazinocarbonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
15 1-*N*-carboxymethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N*-(2-(imidazol-4-yl)ethyl)carbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-hydroxyethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
20 1-(2-aminoethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-methanesulfonylaminoethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
25 1-(2-sulfamylethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-carboethoxyethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
30 1-(2-carboxyethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-*tert*-butoxycarbonylaminoethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
35 1-cyanomethyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,

- 1-carboxymethyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N*-methylcarbamoylmethyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
5 1-(1H-tetrazol-5-ylmethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-methanesulfonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-ethanesulfonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
10 1-phenylsulfonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
15 1-*N,N*-dimethylcarbamoyl-6-phenylmethyl-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-phenylmethyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,  
20 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylsulfonyl}indole,  
25 1-(morpholin-4-ylcarbonyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-(*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thien-2-oyl}indole,  
30 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]fur-2-oyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]thiazo-2-oyl}indole,  
35 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thiazo-2-oyl}indole,

- 1-methyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]phenylsulfonylamino}indole,  
4,7-dimethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
5 4,7-dimethyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
4,7-dimethyl-3-{4-[(3H-2-methylimidazo[4,5-c]pyrid-3-yl)methyl]benzoyl}indole,  
7-benzyloxy-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
7-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
10 6-(4-fluorophenyl)-3-{N-[3-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)propyl]sarcosyl}indole-1-carboxylic acid dimethyl amide,  
1-N,N-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-6-benzyloxy-3-{3-fluoro-4-[(1H-2-methylimidazo-  
15 [4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-4-methoxycarbonyl-3-{5-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole,  
1-N,N-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole hydrochloride,  
20 1-N,N-dimethylcarbamoyl-5-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]phenylsulfonyl}indole,  
1-N,N-dimethylcarbamoyl-4-bromo-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
25 1-N,N-dimethylcarbamoyl-4-acetyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-4-(fur-2-yl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
30 1-N,N-dimethylcarbamoyl-4-(benzo[b]fur-2-yl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-N,N-dimethylcarbamoyl-4-ethynyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
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- 4-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
5 1-*N,N*-dimethylcarbamoyl-4-fluoro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-2-methyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1,4-di-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
10 1-*N,N*-dimethylcarbamoyl-5-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
15 4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
4-methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-benzyloxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
20 1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid,  
1-*N,N*-dimethylcarbamoyl-4(*N*-nonylcarbamoyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
25 1-*N,N*-dimethylcarbamoyl-4-(dec-1-yloxycarbonyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxy-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
30 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)hex-6-ylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole,  
35 4-methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole,

- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)pent-5-ylcarbonyl]indole,
- 1-*N,N*-dimethylcarbamoylmethyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)pent-5-ylcarbonyl]indole,
- 5 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)pent-5-ylcarbonyl]indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(2-methyl-4-(3*H*)quinazolinone-3-yl)methyl]benzoyl}indole,
- 1-(2-ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 10 1-*N,N*-dimethylsulfamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylsulfamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 15 1-acetoxymethyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-(2-propanesulfonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-(1-pinacolyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 20 1-carbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N*-methylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 25 1-(2-ethoxyethyl)-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole,
- 30 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole,
- 35 1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,

- 1-*N,N*-dimethylcarbamoyl-4-hydroxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 5 1-*N,N*-dimethylcarbamoyl-6-(benzo[*b*]fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-6-(fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4(*N,N*-dimethylaminocarbonyloxy)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 10 1-*N,N*-dimethylcarbamoyl-4(*N,N*-dimethylaminocarbonylamino)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-cyano-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride,
- 15 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*b*]pyrid-3-yl)methyl]benzoyl}indole,
- 20 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl]benzoyl}indole,
- 25 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)eth-1-yl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1*H*-imidazo[4.5-*c*]pyrid-1-yl)eth-1-yl]benzoyl}indole,
- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,
- 30 1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,
- 1-(2-ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,
- 35 1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,

- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-(trifluoromethyl)benzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
5 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-4- and 7-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-nitrobenzimidazolyl)methyl]benzoyl}indole,  
10 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5, 6-dichlorobenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole,  
15 1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole,  
1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2, 4, 6-trimethylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole,  
20 1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-5-trifluoromethyl-2-methylmethylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
25 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(4-chloro-1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1,5-*H*-2-methylimidazo[4.5-*c*]pyrid-4-one-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
30 1-*N,N*-dimethylcarbamoyl-4-(2-propyloxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole,  
35 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole, and



1-*N,N*-Dimethylcarbamoyl-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo-  
[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

Particularly preferred compounds of the present invention are

- 1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{3-fluoro-  
4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo-  
[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo-  
[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{4-  
[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole, and  
1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-  
imidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
or a pharmaceutically acceptable salt thereof.

15

#### PAF Inhibitory Activity of the Compounds of the Present Invention

The ability of representative compounds of the present invention to inhibit PAF activity was determined in an *in vitro* test using the following method.

Citrated whole rabbit blood was obtained from Pel-Freez (Rogers, AR).

- 20 Rabbit platelets were prepared by centrifugation and washing. The platelets were lysed by freeze-thawing and sonication; platelet membranes were prepared by centrifugation and washing. Final membrane preparations were stored frozen in 10 mM Tris/5 mM MgCl<sub>2</sub>/2 mM EDTA (TME buffer, pH 7.0) with 0.25 M sucrose added for membrane stabilization.

- 25 The standard PAF receptor binding assay contained 10  $\mu$ g platelet membrane protein, 0.6 nM [<sup>3</sup>H]C<sub>18</sub>-PAF (from Amersham or New England Nuclear; specific activity 120-180 Ci/mmol), with and without test compound, in "binding buffer" consisting of TME with 0.25% bovine serum albumin added (Sigma, RIA grade). The final volume of the assay was 100  $\mu$ l. The assay was conducted in Millititre-GV™ (Millipore Corp.) filtration plates; incubation time was for 60 minutes at room temperature (22-23°C.). "Specific binding" was operationally defined as the arithmetic difference between "total binding" of 0.6 nM [<sup>3</sup>H]C<sub>18</sub>-PAF (in the absence of added PAF) and "nonspecific binding" (in the presence of 1  $\mu$ M PAF). After the prescribed incubation, platelet membranes were filtered under vacuum and washed  
30 with 1 millilitre of "binding buffer". The filters were dried and removed. The bound radioactivity was quantitated with a Berthold TLC-Linear Analyzer model LB2842.

Dose-response curves of inhibition of specific [<sup>3</sup>H]C<sub>18</sub>-PAF binding by test compounds were conducted in triplicate, with at least four doses covering the active range. Experiments were repeated at least once. IC<sub>50</sub> values (concentration producing 50% inhibition) were determined by point-to-point evaluation. K<sub>i</sub> values of inhibitory binding constants were calculated according to the method of Cheng and Prusoff [*Biochem. Pharmacol.* 22 (1973) 3099-3108] whereby

$$\begin{aligned}
 K_i &= \frac{IC_{50}}{1 + ([^3H]PAF)/K_d[^3H]PAF)} \\
 &= \frac{IC_{50}}{1 + (0.6 \text{ nM}/0.6 \text{ nM})} \\
 &= \frac{IC_{50}}{2}
 \end{aligned}$$

The values of K<sub>i</sub> for representative compounds of the present invention appear in Table 1.

Table 1

Example	K <sub>i</sub> (nM) or % Inhibition	Example	K <sub>i</sub> (nM) or % Inhibition
2	56	30	342
3	75	31	44
4	2.3	32	10% @ 1.0 μM
6	140	33	29
7	700	90	2.9
9	60	95	130
10	258	96	7.7
11	86	102	10
12	140	107	0.6
13	150	112	150
14	5	122	0.8
16	18% @ 100 μM	126	62
17	422	131	4.7
18	323	135	1.3
19	280	138	2.2
20	26% @ 100 μM	141	20
22	146	143	0.9

24

23	7% @ 1.0 $\mu$ M	150	40
24	6% @ 1.0 $\mu$ M	156	19
25	14% @ 1.0 $\mu$ M	159	9
26	7% @ 1.0 $\mu$ M	162	14
27	160	167	450
28	87	174	4
29	494		

### Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise one or more of the compounds of formula I above formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form

may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-

lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like.

5 The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

10 Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments, and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being  
15 within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend  
20 upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

25 Generally dosage levels of about 0.001 to about 100 mg, more preferably of about 0.01 to about 20 mg, and most preferably about 0.1 to about 10 mg of active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

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#### Preparation of Compounds of the Invention

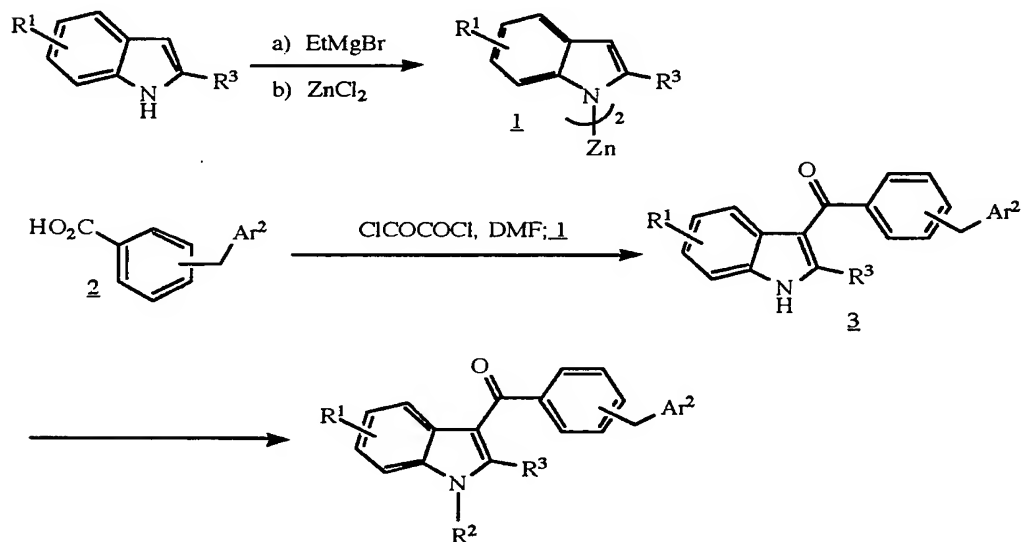
The compounds of this invention can be prepared by a variety of synthetic routes. Representative procedures are outlined as follows. It should be understood that R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and Ar<sup>2</sup> as used herein correspond to the groups identified above.

35 A general route to the compounds of this invention is shown in Scheme 1. Indolyl zinc reagent 1 is prepared by treatment of the corresponding indole with

28

ethylmagnesium bromide and zinc chloride. Conversion of benzoic acid 2 to the acid chloride by reaction with oxalyl chloride, followed by addition of indolyl zinc reagent 1 forms 3, which is converted to the desired final product as described in PCT/US92/05890 (international publication no. WO 93/1813).

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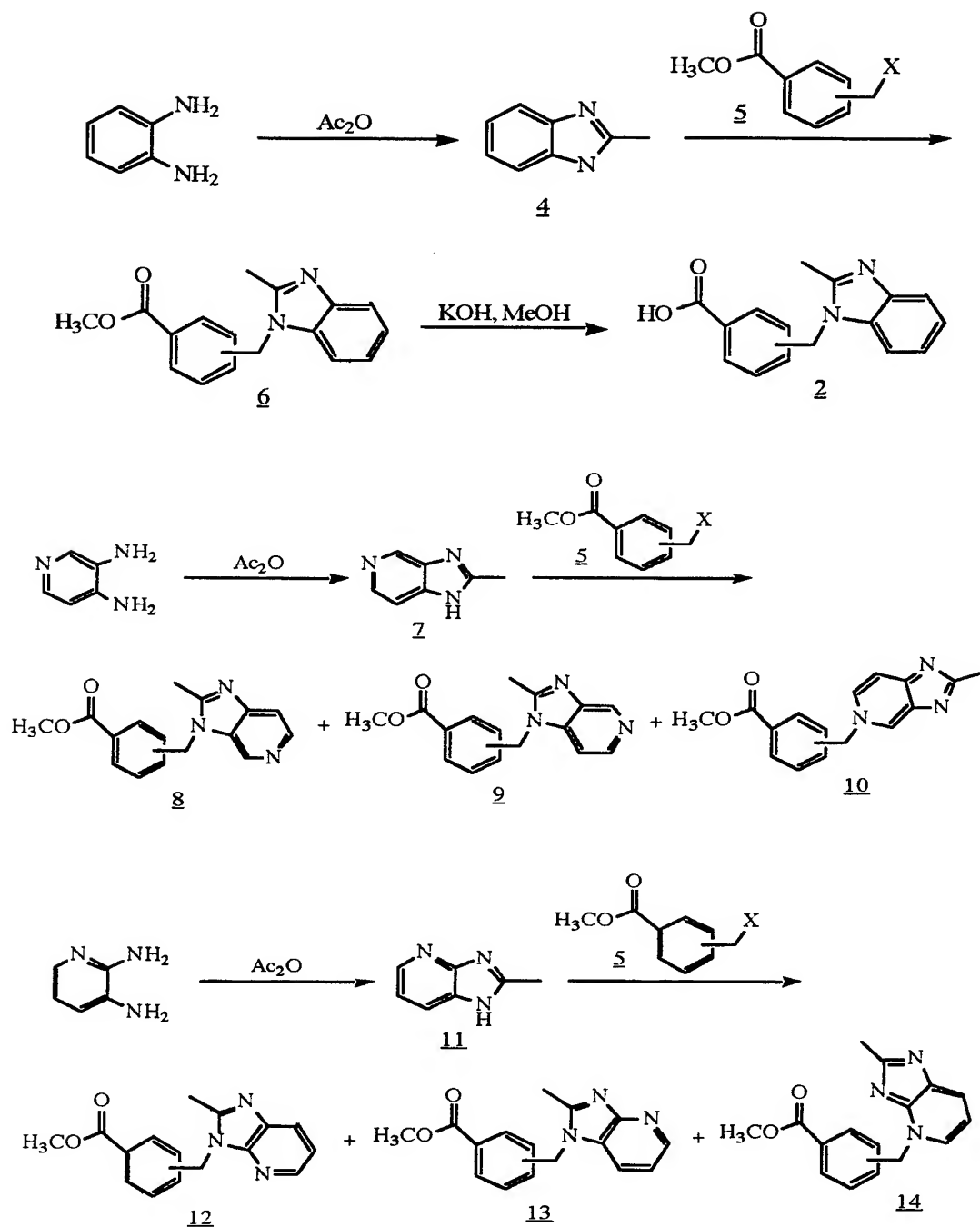
**Scheme 1**

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Preparation of the intermediate benzoic acid 2 is shown in Scheme 2. 1,2-phenylenediamine is condensed with acetic anhydride to form 2-methylbenzimidazole which is then reacted with benzyl halide 5 (where X is Br, Cl, I, methansulfonyl, or p-toluenesulfonyl), in the presence of base to form 6. Hydrolysis of ester 6 gives benzoic acid 2. Condensation of 3,4-diaminopyridine with acetic anhydride followed by reaction with benzyl halide 5 as described above gives a mixture of 1-, 3-, and 5-substituted imidazo[4,5-c]pyridines (compounds 8, 9, and 10) which are separated by chromatography on silica gel and converted to 2 as described above. Similarly, imidazo[4,5-b]pyridines 12, 13, and 14 are prepared from 2,3-diaminopyridine.

29

## Scheme 2

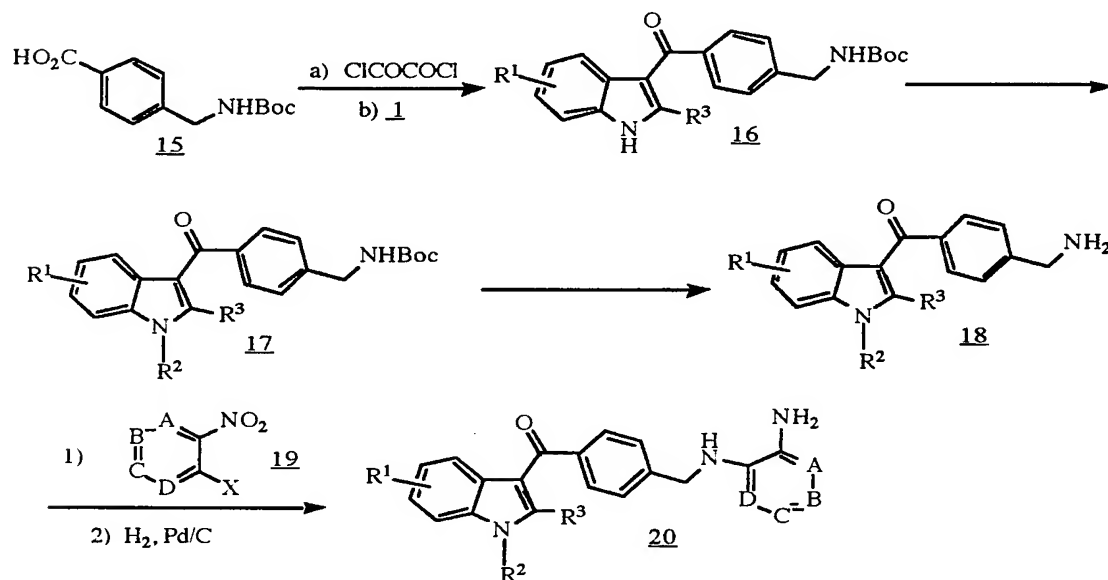




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An alternative procedure for the preparation of the compounds of this invention is shown in Schemes 3a and b. According to Scheme 3a, 4-(*N*-*tert*-butoxycarbonylaminomethyl)benzoic acid 15, prepared by treatment of 4-(aminomethyl)benzoic acid with di-*tert*-butyldicarbonate and base, is converted to the acid chloride and coupled with indolylzinc reagent 1 as described in Scheme 1 to give 16. The group R<sup>2</sup> is then introduced as described in Scheme 1, and the *tert*-butoxycarbonyl group is hydrolyzed with HCl to form amine 18. Reaction of 18 with substituted nitropyridine 19, wherein any one of A, B, C, and D is N, and X is halogen or alkoxy, followed by reduction of the nitro group, preferably by hydrogenolysis catalyzed by palladium on carbon, gives key intermediate 20.

Scheme 3a

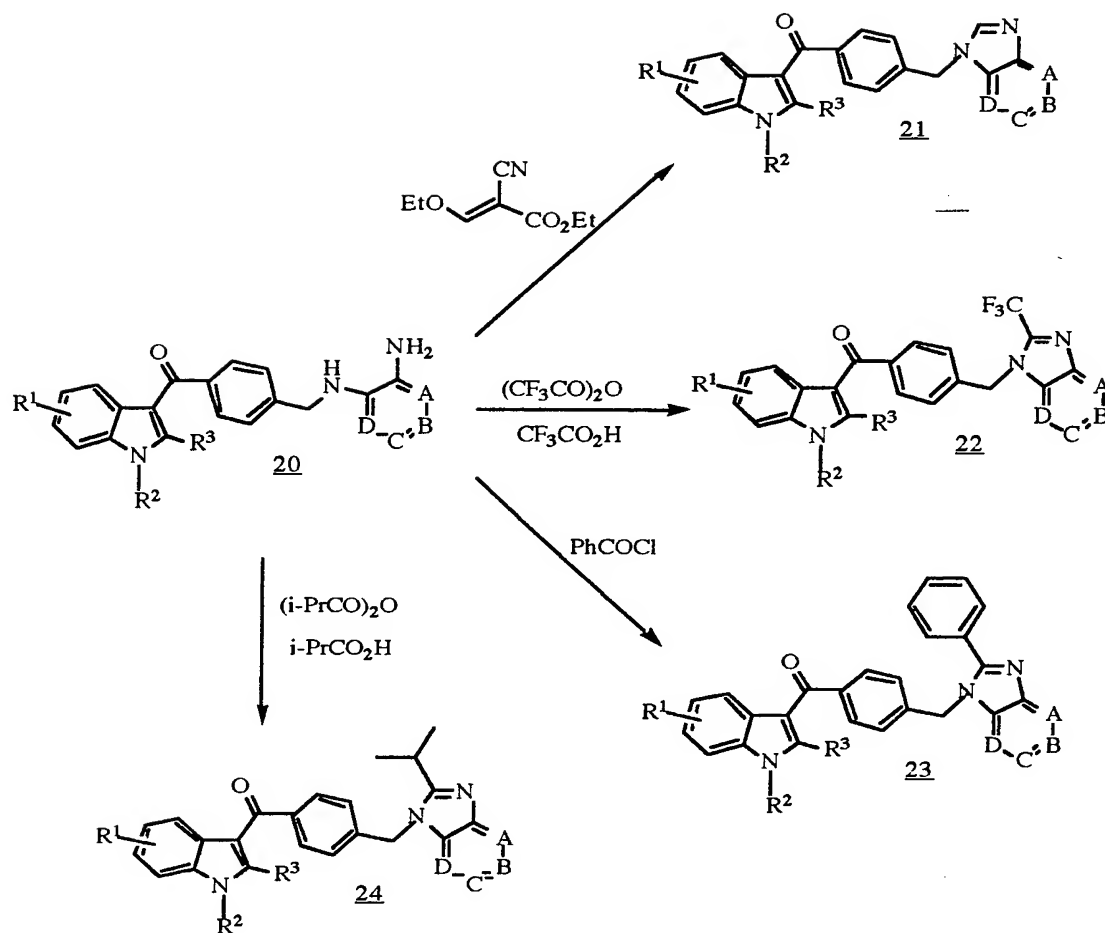


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The conversion of diaminopyridine 20 to the compounds of this invention is shown in Scheme 3b. Reaction of 20 with ethyl(ethoxymethylene)cyanoacetate provides the compounds 21 in which R<sup>13</sup> is H. Introduction of alkyl groups is accomplished by reaction of 20 with the appropriate anhydride as shown in the preparation of compounds 22 and 24. Compounds of formula 23 are prepared by reaction of 20 with benzoyl chloride.

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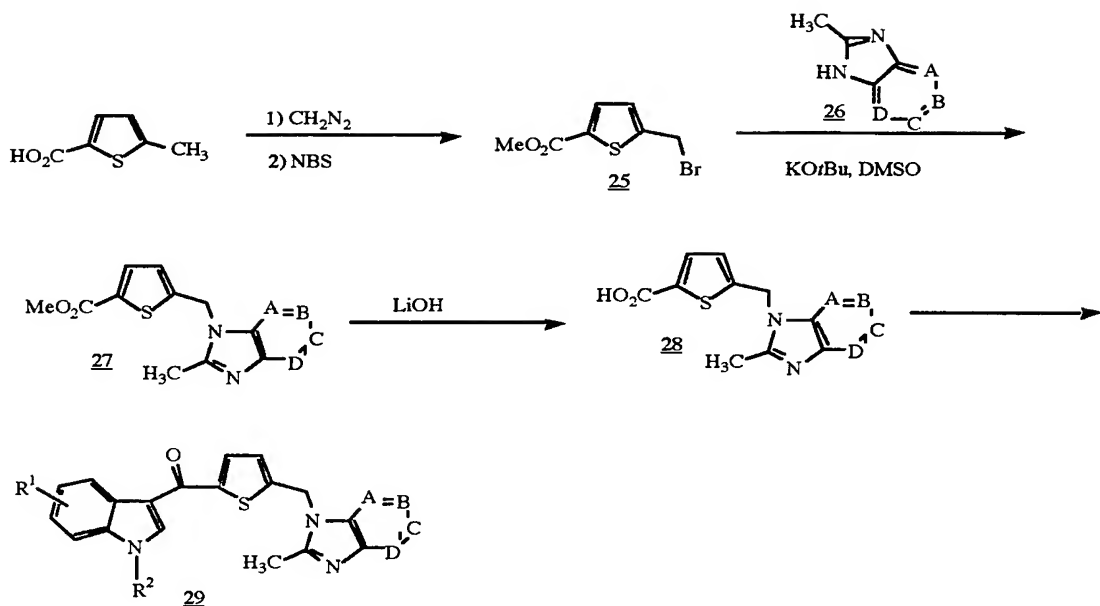
31  
Scheme 3b



- 5           The preparation of the compounds of this invention where Ar<sup>1</sup> is thienyl is shown in Scheme 4. 2-carbomethoxy-5-bromomethylthiophene 25 is prepared from 5-methyl-2-thiophenecarboxylic acid by reaction with diazomethane and *N*-bromosuccinimide. Reaction of imidazopyridine 26, wherein any one of A, B, C, or
- 10       D is N, with bromomethylthiophene 25 in the presence of potassium *tert*-butoxide and DMSO gives 27, which is hydrolzed to thiophenecarboxylic acid 28 with lithium hydroxide. The desired compound 29 is then prepared from 28 as described in Scheme 1 above.

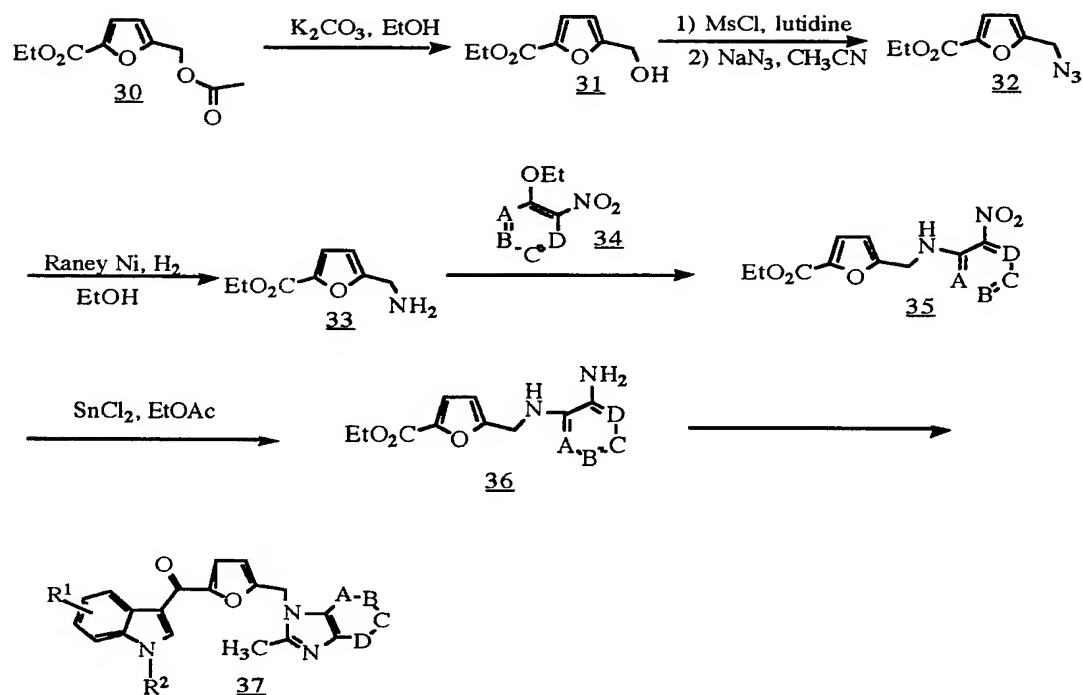
32

## Scheme 4



- 5 The preparation of the compounds of this invention in which  $\text{Ar}^1$  is furyl is shown in Scheme 5. 5-acetoxy-2-carboxyethylfuran **30** is hydrolyzed with potassium carbonate in ethanol to give furyl alcohol **31**, which is converted to furyl azide **32** by treatment with methanesulfonyl chloride and lutidine to give the mesylate, followed by displacement with sodium azide. Raney nickel hydrogenolysis of the azide gives
- 10 amine **33**. Reaction of **33** with ethoxynitropyridine **34**, in which any one of A, B, C, or D is nitrogen, followed by reduction with tin(II) chloride gives diamine **36** which is converted to the desired compound **37** as described in Scheme 3b.

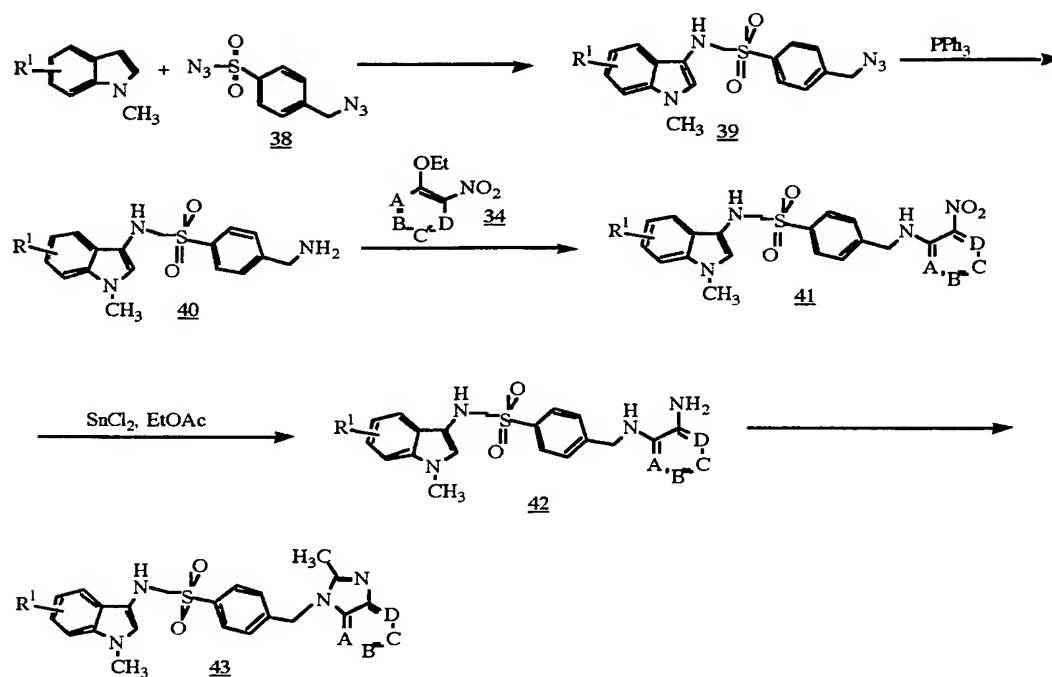
33  
**Scheme 5**



5           The preparation of compounds in which L<sup>1</sup> is sulfonylamino is outlined in Scheme 6. Heating 1-methylindole and 4-azidomethylphenylsulfonyl azide **38**, prepared by reaction of p-toluenesulfonyl chloride with *N*-bromosuccinimide followed by sodium azide, gives azide **39**. Reduction of **39** with triphenylphosphine gives the primary amine **40**. Reaction with ethoxynitropyridine **34**, in which any one of A, B, 10 C, or D is nitrogen, followed by reduction with tin(II) chloride gives diamine **41** which is converted to the desired compound **42** as described in Scheme 3b.

34

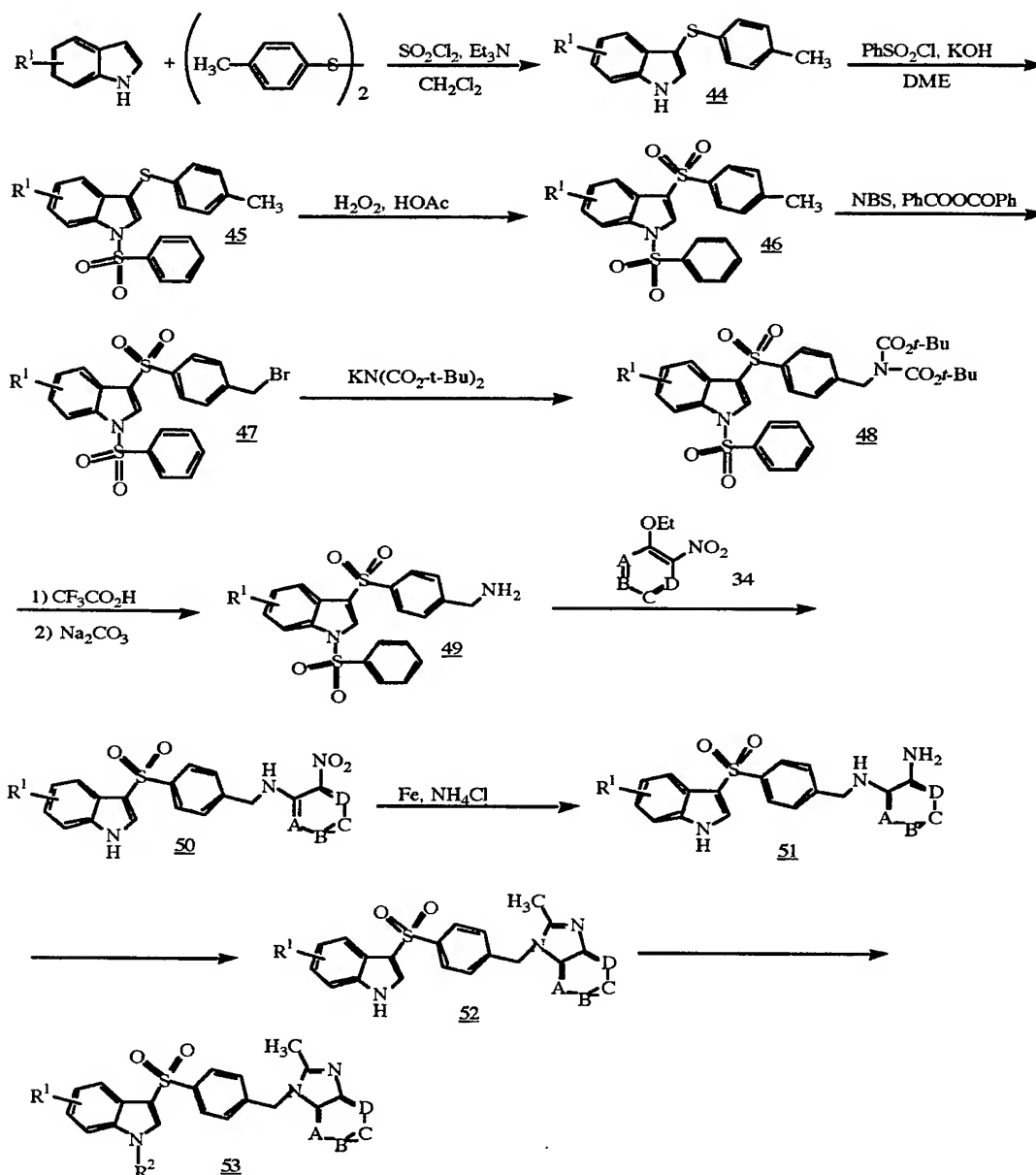
## Scheme 6



- 5 The preparation of compounds in which  $L^1$  is  $-SO_2-$  is shown in Scheme 7. According to Scheme 7, the desired substituted indole is reacted with p-tolyl disulfide and sulfonyl chloride in the presence of triethylamine to form 3-(p-tolylthio)indole **44**. Reaction of **44** with phenylsulfonyl chloride and KOH gives 1-phenylsulfonylindole derivative **45** which is oxidized to **46** with  $H_2O_2$  in acetic acid. Bromination of **46**
- 10 with *N*-bromosuccinimide and benzoyl peroxide gives bromomethyl compound **47**. Displacement of bromide with potassium bis(*t*-butyloxycarbonyl)amide and deprotection with trifluoroacetic acid followed by sodium carbonate gives benzyl amine **49**. Reaction of **49** with ethoxynitropyridine **34**, in which any one of A, B, C, or D is nitrogen, followed by reduction with iron and  $NH_4Cl$  gives diamine **51** which
- 15 is converted to imidazopyridine **52** as described in Scheme 3b. The desired final product **53** is then prepared as described in PCT/US92/05890 (international publication no. WO 93/1813).

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## Scheme 7

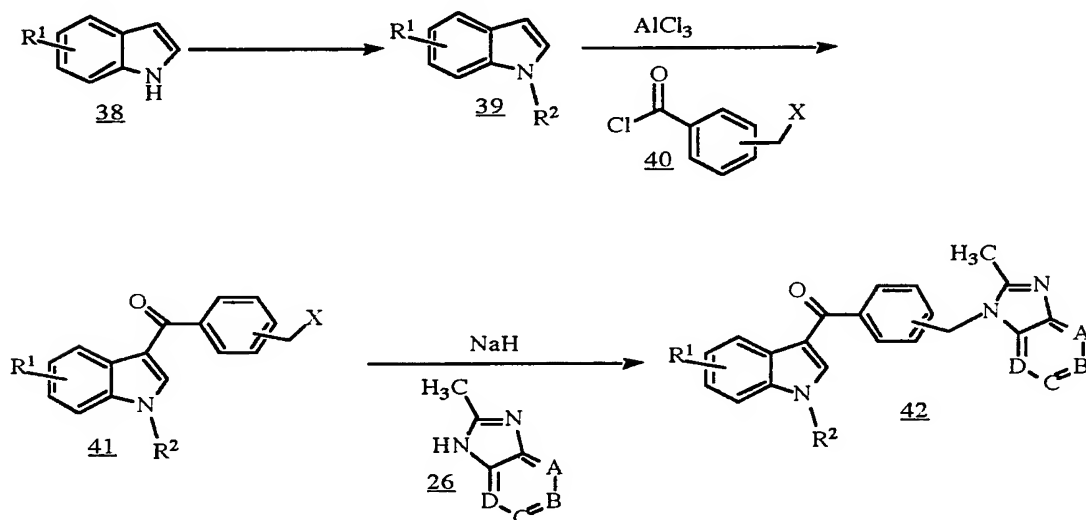


- 5 An alternative synthesis of the compounds of the invention which allows for facile introduction of Ar<sup>2</sup> is shown in Scheme 8. Indole 38 is converted to 1-substituted indole 39 by reaction with base, for example KOH or NaH, and R<sup>2</sup>X (where X is Br, Cl, I, methansulfonyl, or p-toluenesulfonyl). Friedel-Crafts acylation of 39 with benzoyl chloride 40 provides 3-benzoylindole 41. The desired compound

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42 is prepared by reaction of imidazopyridine 26 (where any one of A, B, C, or D is N) or benzimidazole 26 (where A, B, C, and D are CH) with base, for example NaH, followed by alkylation with 41.

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**Scheme 8**

The foregoing may be better understood by the following examples, which are presented for the purpose of illustration and are not intended to limit the scope of the invention.

**Example 1**

Preparation of 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]-benzoyl}indole.

**Step 1: 2-Methylbenzimidazole.**

A solution of 1,2-diaminobenzene (5.00g, 46.3 mmol) in acetic anhydride (36.5 mL) was heated for 17 hours at 90 °C and then stirred for 17 hours at ambient temperature. The reaction mixture was taken to pH 9 by dropwise addition of NH<sub>4</sub>OH, with ice added as necessary to keep the mixture cool, followed by cooling in an ice bath. The resulting precipitate was filtered, rinsed with H<sub>2</sub>O, and dried in a vacuum oven to give 5.28 g of 2-methylbenzimidazole as a brown solid.

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Step 2: Methyl 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate.

To a solution under N<sub>2</sub> of 2-methylbenzimidazole (2.00g, 15.2 mmol), prepared as in step 1, in THF (75.8 mL) was added NaH (437 mg, 18.2 mmol) in one portion. The resulting brown suspension was stirred for one hour at ambient temperature, then cooled to 0 °C and a solution of methyl (4-bromomethyl)benzoate (2.89 g, 12.6 mmol) in THF (14.0 mL) was added dropwise via syringe, after which the ice bath was removed and the reaction mixture was stirred for 17 hours at ambient temperature. The reaction mixture was poured into a mixture of H<sub>2</sub>O and ethyl acetate and the layers were separated. The organic phase was washed twice with H<sub>2</sub>O, and the aqueous phase was washed three times with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave methyl 4-(2-methylbenzimidazol-1-ylmethyl)benzoate (2.82 g) as a yellow solid.

Step 3: 4-(2-Methyl-1H-benzimidazolylmethyl)benzoic acid.

To a solution under N<sub>2</sub> of methyl 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate (2.72 g, 9.71 mmol) in methanol (21.6 mL) was added 1M aqueous KOH (11.7 mL, 11.7 mmol). The reaction mixture was stirred for 1.33 hours at ambient temperature. Aqueous 1M HCl was added until a pH of about 4 was obtained, and the reaction mixture was concentrated *in vacuo*. The residue was cooled in an ice bath for 30 min and filtered. The resulting tan precipitate was dried in the vacuum oven and the filtrate was extracted twice with ethyl acetate and twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a tan solid which was combined with the original precipitate to give 2.51 g of 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoic acid.

Step 4: 6-(4-Fluorophenyl)-3-{4-[(1H-2-methylbenzimidazol-1-yl)methyl]benzoyl}indole.

To a suspension of 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoic acid (1.50 g, 5.63 mmol), prepared as in step 3, in THF (28 mL) was added NaH (195 mg, 8.46 mmol) in a single portion. The reaction mixture was stirred for 10 min, then DMF (85 µL, 1.13 mmol) and oxalyl chloride (953 µL, 11.3 mmol) were added. After stirring for 4 hours at ambient temperature, the reaction mixture was concentrated *in vacuo* to give a gray powder which was placed under N<sub>2</sub> and suspended in CH<sub>2</sub>Cl<sub>2</sub> (30 mL). In a separate flask, ethylmagnesium bromide (3M solution in ether, 4.5 mL, 13.5 mmol) was added to a solution of 6-(4-



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fluorophenyl)indole (2.38 g, 11.3 mmol), prepared as described in WO 93/01813, in CH<sub>2</sub>Cl<sub>2</sub> (56 mL). After 15 min, ZnCl<sub>2</sub> (1.0M solution in ether, 13.5 mL, 13.5 mmol) was added and the clear, dark brown solution was stirred for 20 min at ambient temperature. The 6-(4-fluorophenyl)indolylzinc solution was then transferred via  
5 cannula to the acid chloride suspension and the resulting light-brown suspension was stirred for 20 hours at ambient temperature. The reaction mixture was quenched with H<sub>2</sub>O (20 mL) and filtered. The filtrate layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in*  
10 *vacuo* to give a solid. The filter cake was stirred with methanol and filtered again. The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x50 mL), and the combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give additional solid. The combined solids were purified by chromatography on silica gel (2%, then 5%, then 10% methanol/CH<sub>2</sub>Cl<sub>2</sub> to give 6-(4-  
15 fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole (539 mg) as a red solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 5.61 (s, 2H), 7.15-7.25 (m, 2H), 7.25-7.35 (m, 3H), 7.5-7.6 (m, 6H), 7.97 (d, 1H, J = 3.0 Hz), 8.28 (d, 1H, J = 8.4 Hz), 12.16 (br s, 1H). MS (DCI/NH<sub>3</sub>) m/e 460 (M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>22</sub>FN<sub>3</sub>O · 0.6H<sub>2</sub>O: C, 76.61; H, 4.97; N, 8.93. Found: C, 76.72; H, 4.90;  
20 N, 8.95.

### Example 2

#### Preparation of 1-N,N-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole.

25 To a solution of 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole (200 mg, 0.44 mmol), prepared as in Example 1, in 1:1 THF/DMF (8.0 mL) at 0 °C was added KOH (61 mg, 1.09 mmol). The reaction mixture was stirred for 10 min and dimethylcarbamoyl chloride (60.3 μL, 0.65 mmol) was added via syringe. Stirring was continued for 40 min and then  
30 the reaction mixture was partitioned between H<sub>2</sub>O (20 mL) and ethyl acetate (20 mL). The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Pure 6-(4-fluorophenyl)-3-{4-[1H-2-methylbenzimidazolyl)methyl]benzoyl}indole-1-carboxylic acid dimethylamide (200  
35 mg) was obtained by chromatography on silica gel (5% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.56 (s, 3H), 3.02 (s, 6H), 5.62 (s, 2H), 7.15-7.25 (m,

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2H), 7.25-7.35 (m, 4H), 7.5-7.6 (m, 2H), 7.64 (dd, 1H, J = 8.4, 1.8 Hz), 7.7-7.8 (m, 2H), 7.8-7.9 (m, 3H), 8.15 (s, 1H), 8.30 (d, 1H, J = 8.4 Hz). MS (DCI/NH<sub>3</sub>) m/e 531 (M+H)<sup>+</sup>. Anal calcd for C<sub>33</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>2</sub> · 0.4H<sub>2</sub>O: C, 73.70; H, 5.21; N, 10.42. Found: C, 73.70; H, 5.30; N, 10.40.

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### Example 3

Preparation of 6-(4-Fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 1H-2-Methylimidazo[4,5-c]pyridine.

10       The desired compound was prepared according to the method of Example 1, step 1, except substituting 3,4-diaminopyridine for 1,2-diaminobenzene.

Step 2: Methyl 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate.

15       To a solution under N<sub>2</sub> of 1H-2-methylimidazo[4,5-c]pyridine (600 mg, 4.51 mmol), prepared as in step 1, in THF (33 mL) and DMF (11 mL) was added NaH (130 mg, 5.41 mmol) in a single portion. The resulting brown suspension was stirred for one hour at ambient temperature, then cooled to 0 °C and a solution of methyl 4-(bromomethyl)benzoate (1.03 g, 4.51 mmol) in THF (5 mL) was added via syringe. The cold bath was then removed and the reaction mixture stirred for 17 hours at  
20       ambient temperature. The reaction mixture was partitioned between pH 7 buffer (40 mL), and ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (2x30 mL), and the combined organic layers were washed with H<sub>2</sub>O (5x30 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a mixture of  
25       predominately two products. Chromatography on silica gel gave methyl 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate (150 mg) and methyl 4-(3H-2-methylimidazo[4,5-c]pyrid-3-ylmethyl)benzoate (95 mg). The original aqueous phase was concentrated *in vacuo* to give a brown solid which was taken up in methanol, dried over MgSO<sub>4</sub>, filtered, and re-concentrated *in vacuo*. Chromatography on silica  
30       gel gave methyl 4-(5H-2-methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoate (435 mg).

Step 3: 6-(4-Fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

35       The desired compound was prepared according to the method of Example 1, steps 3 and 4, except substituting 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate, prepared as in step 2, for methyl 4-(2-methylbenzimidazol-1-ylmethyl)benzoate. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 5.65 (s, 2H),

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7.25-7.35 (m, 4H), 7.52 (dd, 1H,  $J = 8.4, 1.5$  Hz), 7.64 (d, 1H,  $J = 8.7$  Hz), 7.7-7.8 (m, 3H), 7.80 (d, 1H,  $J = 8.1$  Hz), 7.97 (s, 1H), 8.28 (d, 1H,  $J = 8.4$  Hz), 8.32 (d, 1H,  $J = 5.4$  Hz), 8.87 (s, 1H), 12.15 (br s, 1H). MS (FAB)  $m/e$  461 ( $M+1$ )<sup>+</sup>.

Anal calcd for  $C_{29}H_{21}FN_4O \cdot 1.2H_2O$ : C, 72.25; H, 4.89; N, 11.62. Found: C, 72.26; H, 4.72; N, 11.67.

#### Example 4

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

10 Step 1: 6-(4-fluorophenyl)indole-1-carboxylic acid dimethylamide.

To a 0 °C solution of 6-(4-fluorophenyl)indole (2.00 g, 9.48 mmol), prepared as described in WO 93/01813, in THF (50 mL) was added KOH (2.7 g, 47.4 mmol) in a single portion and the cold bath was removed. After stirring for 15 min at ambient temperature, dimethylcarbamoyl chloride (1.3 mL, 14.2 mmol) was added via  
15 syringe and the resulting brown suspension was stirred for 4 hours at ambient temperature. The reaction mixture was poured into a mixture of ethyl acetate and saturated aqueous  $NH_4Cl$  and the layers were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over  $MgSO_4$ , filtered, and concentrated *in vacuo* to afford 6-(4-fluorophenyl)indole-1-  
20 carboxylic acid dimethylamide as a brown solid which was used without further purification.

Step 2: 6-(4-Fluorophenyl)-3-(4-chloromethylbenzoyl)indole-1-carboxylic acid dimethylamide.

25 To a solution of 4-(chloromethyl)benzoyl chloride (804 mg, 4.26 mmol) in  $CH_2Cl_2$  (21 mL) was added  $AlCl_3$  (850 mg, 6.39 mmol) in a single portion, and the yellow solution was stirred for 15 min at ambient temperature. A solution of 6-(4-fluorophenyl)indole-1-carboxylic acid dimethylamide (1.00 g, 3.55 mmol), prepared as in step 1, in  $CH_2Cl_2$  was added dropwise and the dark solution was stirred for 2  
30 hours at ambient temperature. Additional  $AlCl_3$  (0.24 g, 1.78 mmol) was added and the reaction mixture was stirred for 0.5 hours. The reaction mixture was poured into a separatory funnel containing ice water and  $CH_2Cl_2$ . The layers were separated and the aqueous phase was extracted three times with  $CH_2Cl_2$ . The combined organic layers were washed with saturated aqueous  $NaHCO_3$ , dried over  $MgSO_4$ , filtered,  
35 and concentrated *in vacuo*. Pure 6-(4-fluorophenyl)-3-(4-

chloromethylbenzoyl)indole-1-carboxylic acid dimethylamide (294 mg) was obtained by chromatography on silica gel (25%, then 50% ethyl acetate/hexanes).

Step 3: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a solution of imidazo[4,5-*c*]pyridine (407 mg, 3.06 mmol) in THF (15 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-1*H*-pyrimidinone (5 mL) was added NaH (110 mg, 4.59 mmol) in a single portion and the resulting solution was stirred for 1 hour at ambient temperature. In a separate flask, NaBr (630 mg, 6.11 mmol) was added to a solution of 6-(4-fluorophenyl)-3-(4-chloromethylbenzoyl)indole-1-carboxylic acid dimethylamide (1.33 g, 3.06 mmol), prepared as in step 2, in THF (15 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-1*H*-pyrimidinone (5 mL). The resulting yellow suspension was stirred for 1 hour at ambient temperature, after which the imidazopyridine solution was added dropwise via syringe. The reaction mixture was stirred for 3 hours at ambient temperature and then was partitioned between brine and ethyl acetate. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed twice with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (2%, then 4% methanol/CH<sub>2</sub>Cl<sub>2</sub>) provided 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole. (228 mg). mp 257-259 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.03 (s, 6H), 5.67 (s, 2H), 7.25-7.35 (m, 4H), 7.6-7.7 (m, 2H), 7.7-7.8 (m, 2H), 7.8-7.9 (m, 3H), 8.15 (s, 1H), 8.30 (d, 1H, *J* = 8.4 Hz), 8.31 (d, 1H, *J* = 5.7 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 532 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>2</sub> · 0.8H<sub>2</sub>O: C, 70.39; H, 5.09; N, 12.83. Found: C, 70.38; H, 5.39; N, 12.82.

### Example 5

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride.

To a 0 °C solution of 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (50 mg, 0.09 mmol), prepared as in Example 4, in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added 2 mL of 4*N* HCl in dioxane. The resulting yellow solution, which also contained a small amount of yellow oil, was stirred for 15 min at 0 °C and then was concentrated *in vacuo*. CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added to the oily residue and the mixture was sonicated until a fine suspension was obtained. The suspension was diluted with ether and filtered to give 42 mg of 1-*N,N*-

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dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole hydrochloride as a yellow solid. mp 275-278 °C. <sup>1</sup>H NMR (D<sub>3</sub>COD, 300 MHz) δ 2.79 (s, 3H), 3.11 (s, 6H), 5.84 (s, 2H), 7.15-7.25 (m, 2H), 7.40 (apparent d, 2H, J = 8.1 Hz), 7.61 (dd, 1H, J = 8.4, 2.3 Hz), 7.65-7.75 (m, 2H), 7.75-7.80 (narrow m, 1H), 7.85-7.90 (m, 2H), 7.99 (s, 1H), 8.19 (d, 1H, J = 6.3 Hz), 8.34 (d, 1H, J = 8.1 Hz), 8.58 (d, 1H, J = 6.3 Hz), 9.26 (s, 1H). Anal calcd for C<sub>32</sub>H<sub>27</sub>FN<sub>5</sub>O<sub>2</sub>Cl · 0.6H<sub>2</sub>O: C, 66.40; H, 4.91; N, 12.10. Found: C, 66.40; H, 5.00; N, 12.01.

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### Example 6

Preparation of 6-(4-Fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

Step 1: Potassium 4-(3H-2-methylimidazo[4.5-c]pyrid-3-ylmethyl)benzoate.

Hydrolysis of methyl 4-(3H-2-methylimidazo[4.5-c]pyrid-3-ylmethyl)benzoate, prepared as in Example 3, step 2, with aqueous KOH in methanol was accomplished as described in Example 1, step 3. After complete consumption of starting material, the reaction mixture was partitioned between H<sub>2</sub>O and ethyl acetate. The aqueous phase was washed twice with ethyl acetate and concentrated *in vacuo*. Lyophilization of the crude product gave potassium 4-(3H-2-methylimidazo[4.5-c]pyrid-3-ylmethyl)benzoate.

Step 2: 6-(4-Fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

To a suspension of potassium 4-(3H-2-methylimidazo[4.5-c]pyrid-3-ylmethyl)benzoate (350 mg, 1.15 mmol), prepared as in step 1, in THF (6 mL) was added DMF (179 μL, 2.3 mmol) and oxalyl chloride (200 μL, 2.30 mmol). The reddish suspension was stirred at ambient temperature for 1.5 hours after gas evolution ceased. The reaction mixture was concentrated *in vacuo* to give a tan paste which was suspended in CH<sub>2</sub>Cl<sub>2</sub> (6 mL). A solution of 6-(4-fluorophenyl)indolylzinc (2.30 mmol), prepared as described in Example 1, step 4, was added via cannula and the resulting tan suspension was stirred for 17 hours at ambient temperature. The reaction mixture was quenched with H<sub>2</sub>O (50 mL) and the layers were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL) and ethyl acetate (4x50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (2%, then 5%, then 7% methanol/CH<sub>2</sub>Cl<sub>2</sub> gave 79 mg of 6-(4-fluorophenyl)-3-{4-[(3H-2-

methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 5.64 (s, 2H), 7.2-7.3 (m, 4H), 7.45-7.55 (m, 1H), 7.63 (dd, 1H, J = 5.4, 1.1 Hz), 7.75-7.80 (m, 2H), 7.91 (s, 1H), 8.2-8.3 (m, 1H), 8.31 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H), 12.08 (br s, 1H). MS (FAB) m/e 461 (M+1)<sup>+</sup>.

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### Example 7

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole, prepared as in Example 6, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.63 (s, 3H), 3.03 (s, 6H), 5.73 (s, 2H), 7.25-7.40 (m, 4H), 7.59 (dd, 1H, J = 5.7, 1.0 Hz), 7.65 (dd, 1H, J = 8.1, 1.5 Hz), 7.7-7.8 (m, 2H), 7.8-7.9 (m, 3H), 8.16 (s, 1H), 8.30 (d, J = 8.1 Hz), 8.31 (d, 1H, J = 5.7 Hz), 8.97 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 532 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>2</sub> · 0.9H<sub>2</sub>O: C, 70.16; H, 5.11; N, 12.78. Found C, 70.29; H, 5.28; N, 12.27.

### Example 8

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole.

Step 1: 6-(4-Fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole.

The desired compound was prepared according to the method of Example 6, except substituting 4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoate, prepared as in Example 3, step 2, for methyl 4-(3H-2-methylimidazo[4.5-c]pyrid-3-ylmethyl)benzoate.

Step 2: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole.

The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole, prepared as in step 1, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.02 (s, 6H), 5.77 (s, 2H), 7.25-7.35 (m, 2H), 7.57 (apparent d, 2H, J = 8.4 Hz), 7.6-7.7 (m, 2H), 7.7-7.8 (m, 2H), 7.80-7.85 (narrow m, 1H), 7.89

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(apparent d, 2H, J = 8.4 Hz), 8.16 (s, 1H), 8.21 (dd, 1H, J = 6.9, 1.8 Hz), 8.31 (d, 1H, 8.4 Hz), 9.00 (d, 1H, J = 1.2 Hz). MS (DCI/NH<sub>3</sub>) m/e 532 (M+H)<sup>+</sup>.

### Example 9

5 Preparation of 6-(4-Fluorophenyl)-3-[4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]indole.

Step 1: 4-(N-3-nitropyrid-4-ylamino)benzonitrile.

To a solution under N<sub>2</sub> of 3-nitro-4-chloropyridine (4.63g, 29.2 mmol), prepared as described by Wright, G. C., *J. Heterocyclic Chem.* **1976**, 13, 601, and  
10 Kruger, S. and Mann, F.G., *J. Chem. Soc.* **2 1955**, 758, in absolute ethanol (100 mL) was added 4-aminobenzonitrile (3.45 g, 29.2 mmol) and the resulting purple-brown solution was stirred for 17 hours at ambient temperature, during which time it became a green-brown suspension. The reaction mixture was poured into cold 10% aqueous NH<sub>4</sub>OH and filtered. The solid was suspended in ethanol (75 mL) and  
15 heated for 10 min on the steam bath. The suspension was cooled to ambient temperature and filtered to give 4-(N-3-nitropyrid-4-ylamino)benzonitrile as a bright-yellow solid.

Step 2: 4-(N-3-Aminopyrid-4-ylamino)benzonitrile.

20 Catalytic hydrogenation (2 atm H<sub>2</sub>, 10% Pd/C) of 4-(N-3-nitropyrid-4-ylamino)benzonitrile (6.17 g) in 1:1 methanol/CH<sub>2</sub>Cl<sub>2</sub> gave 4-(N-3-aminopyrid-4-ylamino)benzonitrile.

Step 3: 4-(1H-2-Methylimidazo[4,5-c]pyrid-1-yl)benzonitrile.

25 A mixture of 4-(N-3-aminopyrid-4-ylamino)benzonitrile (5.20 g, 24.7 mmol), prepared as in step 2, acetic anhydride (16 mL, 169 mmol), and acetic acid (16 mL) was warmed to 95 °C and stirred for 2 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was azeotroped with benzene to give a brown solid. The brown solid was mixed with 10% aqueous  
30 NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x75 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (6.38 g) as a yellow solid which was used without further purification.

Step 4: Methyl 4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoate.

HCl gas was bubbled for 10 minutes into a flask containing 100 mL of methanol and cooled in an ice/acetone bath, during which time the solution temperature rose to 37 °C. The solution temperature was allowed to come down to -5 °C and a solution of 4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (5.30 g, 22.6 mmol) in methanol (50 mL) was added dropwise over 15 min. The reaction was warmed slowly to ambient temperature and stirred for 65 hours. The milky white reaction mixture was cooled in an ice/water bath and H<sub>2</sub>O (100 mL) was added dropwise. The resulting clear-yellow suspension was stirred for 3 hours at ambient temperature and again cooled in an ice/water bath. Solid Na<sub>2</sub>CO<sub>3</sub> was added until a pH of 8 was achieved and the white suspension was warmed to ambient temperature. Water was added until a clear solution was obtained and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x600 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give methyl 4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoate (5.19 g) as a yellow-white solid.

Step 5: 6-(4-Fluorophenyl)-3-[4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]indole.

The desired compound was prepared according to the method of Example 1, steps 3 and 4, except substituting 4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoate for methyl 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.66 (s, 3H), 7.65 (d, 1H, J = 1.5 Hz), 7.69 (d, 1H, J = 1.5 Hz), 7.82-7.91 (c, 3H), 8.05 (bs, 1H), 8.25 (s, 1H), 8.28 (s, 1H), 8.36 (s, 1H), 8.55 (d, 1H, J = 6 Hz), 8.69-8.80 (c, 5H), 9.24 (s, 1H). IR (KBr) 3140, 1600, 1560, 1500, 1470, 1450, 1430, 1400, 1380, 13250, 1300, 1250, 1230, 1200, 890, 850, 810, 710. MS (DCI/NH<sub>3</sub>) m/e 447 (M+H)<sup>+</sup>, 281, 238, 212, 130, 117 cm<sup>-1</sup>. Anal calcd for C<sub>28</sub>H<sub>22</sub>FN<sub>4</sub>O<sub>2.5</sub>: C, 71.02; H, 4.68; N, 11.84. Found: C, 70.86; H, 4.65; N, 12.26.

**Example 10**

Preparation of 1-N,N-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]indole.

The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]indole, prepared as in Example 9, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole, and using K<sub>2</sub>CO<sub>3</sub>/DMSO instead of



KOH/THF,DMF. mp 307.0-307.5 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.10 (s, 6H), 7.30-7.40 (c, 2H), 7.61-7.72 (c, 2H), 7.73-7.88 (c, 5H), 8.05-8.16 (c, 2H), 8.30-8.41 (c, 2H), 8.96 (s, 1H), 9.08 (bd, 1H, J = 10.5 Hz). IR (KBr) 1700, 1640, 1600, 1520, 1480, 1440, 1390, 1220, 1180, 1090, 1020, 990, 920 cm<sup>-1</sup>. MS (DCI/NH<sub>3</sub>) m/e 518 (M+H)<sup>+</sup>.

### Example 11

#### Preparation of 6-(4-Fluorophenyl)-3-{3-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

##### 10 Step 1: Methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate.

To a solution of 1H-2-methylimidazo[4,5-c]pyridine (3.00 g, 22.5 mmol), prepared as in Example 3, step 1, in THF (165 mL) was added DMF (55 mL) and NaH (95%, 650 mg, 27.0 mmol). The resulting brown suspension was stirred for 1 hour at ambient temperature, then cooled in an ice bath and a solution of methyl 3-(bromomethyl)benzoate (5.18 g, 22.6 mmol) in THF (25 mL) was added dropwise over 10 min. The reaction mixture was stirred for 15 min at 0 °C, then the cold bath was removed and stirring was continued at ambient temperature for 17 hours. The reaction mixture was poured into H<sub>2</sub>O (200 mL) and the aqueous phase was extracted with ethyl acetate (3x250 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 3.95 g of gummy solid. Chromatography on silica gel (2%, then 4%, then 10% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate (620 mg), methyl 3-(3H-2-methylimidazo[4,5-c]pyrid-3-ylmethyl)benzoate (790 mg), and methyl 3-(5H-2-methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoate (1.50 g).

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##### Step 2: 6-(4-Fluorophenyl)-3-{3-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 1, steps 3 and 4, except substituting methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate, prepared as in step 1, for 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate. mp 194.4-196.4 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 5.65 (s, 2H), 7.27-7.38 (c, 3H), 7.49-7.56 (c, 2H), 7.70-7.79 (c, 4H), 7.89 (d, 1H, J = 3 Hz), 8.24 (d, 1H, J = 9 Hz), 8.30 (d, 1H, J = 6 Hz), 8.85 (bs, 1H), 12.16 (bs, 1H). IR (KBr) 3160, 2940, 1610, 1580, 1510, 1450, 1400, 1370, 1290, 1240, 1180, 1160, 1040, 920, 900, 840, 810. MS (DCI/NH<sub>3</sub>) m/e 461(M+H)<sup>+</sup>,

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212, 134  $\text{cm}^{-1}$ . Anal calcd. for  $\text{C}_{29}\text{H}_{21}\text{FN}_4\text{O} \cdot 1.25 \text{H}_2\text{O}$ : C, 72.11; H, 4.9; N, 11.6. Found: C, 72.01; H, 5.17; N, 11.27.

### Example 12

5 Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution under  $\text{N}_2$  of 6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole (921 mg, 2.00 mmol), prepared as in Example 11, in DMSO (2.0 mL), was added  $\text{K}_2\text{CO}_3$  (138 mg, 1.00 mmol) and the resulting dark-yellow suspension was stirred for 30 min at ambient temperature. *N,N*-dimethylcarbamoyl chloride (36.7  $\mu\text{L}$ , 4.00 mmol) was added and stirring was continued for 17 hours. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (0.60 mL), stirred for 30 min, and concentrated to dryness *in vacuo*. The residue was partitioned between saturated aqueous  $\text{NH}_4\text{Cl}$  and  $\text{CH}_2\text{Cl}_2$ . A small amount of brine was added and the layers were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Chromatography on silica gel (3% methanol/ $\text{CH}_2\text{Cl}_2$ ) gave 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (89 mg, 84%). mp. 244.5-245.5  $^\circ\text{C}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.58 (s, 3H), 3.03 (s, 6H), 5.65 (bs, 2H), 7.32 (t, 2H,  $J = 7.5 \text{ Hz}$ ), 7.40 (bd, 1H,  $J = 7.5 \text{ Hz}$ ), 7.56 (bt, 1H,  $J = 7.5 \text{ Hz}$ ), 7.59-7.67 (c, 3H), 7.73-7.83 (c, 4H), 8.02 (s, 1H), 8.24-8.31 (c, 2H), 8.85 (bs, 1H). IR (KBr) 3440, 1700, 1630, 1610, 1580, 1550, 1510, 1480, 1430, 1390, 1230, 1180, 820  $\text{cm}^{-1}$ . MS (DCI/ $\text{NH}_3$ )  $m/e$  532 ( $\text{M}+\text{H}^+$ ), 134, 106. Anal calcd for  $\text{C}_{32}\text{H}_{27}\text{FN}_5\text{O}_2 \cdot 2\text{H}_2\text{O}$ : C, 67.7; H, 5.32; N, 12.34. Found C, 67.78; H, 4.93; N, 12.18.

### Example 13

Preparation of 3-{4-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: potassium 4-(1H-2-methylimidazo[4.5-c]pyrid-1-ylmethyl)benzoate.

30 The desired compound was prepared as described in Example 6, step 1, except substituting methyl 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate, prepared as in Example 3, step 2, for 4-(3H-2-methylimidazo[4,5-c]pyrid-3-ylmethyl)benzoate.

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Step 2: 6-3-{4-[(1H-2-Methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 6, step 2, except substituting potassium 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate, prepared as in step 1, for potassium 4-(3H-2-methylimidazo[4,5-c]pyrid-3-ylmethyl)benzoate, and preparing the indolylzinc reagent from indole instead of 6-(4-fluorophenyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 5.64 (s, 2H), 7.2-7.3 (m, 4H), 7.45-7.55 (m, 1H), 7.63 (dd, 1H, J = 5.4, 1.1 Hz), 7.75-7.80 (m, 2H), 7.91 (s, 1H), 8.2-8.3 (m, 1H), 8.31 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H), 12.08 (br s, 1H). MS (FAB) m/e 367 (M+1)<sup>+</sup>.

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**Example 14**Preparation of 1-N,N-Dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 3-[4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoyl]indole, prepared as in Example 13, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.00 (s, 6H), 5.66 (s, 2H), 7.25-7.45 (m, 4H), 7.6-7.7 (m, 2H), 7.8-7.9 (m, 2H), 8.10 (s, 1H), 8.2-8.3 (m, 1H), 8.31 (d, 1H, J = 5.7 Hz), 8.87 (s, 1H). MS (FAB) m/e 438 (M+1)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub> · 0.7H<sub>2</sub>O: C, 69.38; H, 5.46; N, 15.56. Found: C, 69.69; H, 5.60; N, 14.96.

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**Example 15**Preparation of 3-[4-(5H-2-Methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoyl]indole.

The desired compound was prepared according to the method of Example 1, steps 3 and 4, except substituting methyl 4-(5H-2-methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoate, prepared as in Example 3, step 2, for methyl 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate, and substituting indolylzinc for 6-(4-fluorophenyl)indolylzinc. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.55 (s, 3H), 5.81 (s, 2H), 7.2-7.3 (m, 2H), 7.50-7.55 (m, 1H), 7.56 (d, 2H, J = 8.1 Hz), 7.71 (d, 1H, J = 6.6 Hz), 7.81 (d, 2H, J = 8.7 Hz), 7.91 (d, 1H, J = 3.0 Hz), 8.2-8.3 (m, 1H), 8.32 (dd, 1H, J = 6.6, 1.5 Hz), 12.21 (br s, 1H). MS (DCI/NH<sub>3</sub>) m/e 367 (M+H)<sup>+</sup>.

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**Example 16**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole.

The desired compound was prepared according to the method of Example 2, except substituting 3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole, prepared as in Example 15, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.00 (s, 6H), 5.76 (s, 2H), 7.3-7.4 (m, 2H), 7.5-7.65 (m, 4H), 7.8-7.9 (m, 2H), 8.11 (s, 1H), 8.15-8.30 (m, 2H), 8.99 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 438 (M+H)<sup>+</sup>.

**Example 17**Preparation of 3-{3-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 1, steps 3 and 4, except substituting methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate, prepared as in Example 11, step 1, for 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoate, and preparing the indolylzinc reagent from indole instead of 6-(4-fluorophenyl)indole. mp 246.1-247.3 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 5.64 (s, 2H), 7.19-7.30 (c, 2H), 7.32(bd, 1H, J = 7.5 Hz), 7.48-7.54 (c, 2H), 7.57 (bs, 1H), 7.62 (dd, 1H, J = 6.1 Hz), 7.72 (bd, 1H, J = 7.5 Hz), 7.83 (s, 1H), 8.18-8.22 (c, 1H), 8.30 (d, 1H, J = 6 Hz), 8.85 (s, 1H), 12.06 (bs, 1H). IR (KBr) 1610, 1580, 1520, 1490, 1440, 1390, 1370, 1340, 1290, 1180, 1170, 1150, 1030, 890, 830, 750 cm<sup>-1</sup>. MS (DCI/NH<sub>3</sub>) m/e 367 (M+H)<sup>+</sup>, 118.

**Example 18**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 17, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. mp 192-194 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.01 (s, 6H), 5.64 (s, 2H), 7.32-7.43 (c, 3H), 7.51-7.66 (c, 4H), 7.79 (bd, 1H, J = 7.5 Hz), 7.98 (s, 1H), 8.21-8.32 (c, 2H), 8.85 (bs, 1H). IR (KBr) 3440, 1700, 1630, 1610, 1580, 1530, 1480, 1450, 1390,

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1230, 1180, 1160, 1080, 1030, 760  $\text{cm}^{-1}$ . MS (DCI/ $\text{NH}_3$ )  $m/e$  438 ( $\text{M}+\text{H}$ )<sup>+</sup>, 296, 118.

### Example 19

5 Preparation of 3-{3-[(3H-2-Methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 17, except substituting methyl 3-(3H-2-methylimidazo[4,5-c]pyrid-3-ylmethyl)benzoate, prepared as in Example 11, step 1, for methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)benzoate. mp 210-212 °C. <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.63 (s, 3H), 5.71 (s, 2H), 7.20-7.30 (c, 2H), 7.37 (bd, 1H, J = 7.5 Hz), 7.49-7.59 (c, 3H), 7.60 (bs, 1H), 7.72 (bd, 1H, J = 7.5 Hz), 7.84 (s, 1H), 8.19-8.25 (c, 1H), 8.30 (d, 1H, J = 6 Hz), 8.88 (s, 1H), 12.09 (bs, 1H). IR (KBr) 1610, 1580, 1520, 1510, 1470, 1460, 1450, 1400, 1370, 1310, 1230, 1170, 830, 750  $\text{cm}^{-1}$ . MS (DCI/ $\text{NH}_3$ )  $m/e$  367 ( $\text{M}+\text{H}$ )<sup>+</sup>, 134, 118. Anal calcd for  $\text{C}_{23}\text{H}_{19.5}\text{N}_4\text{O}_{1.75}$ : C, 72.7; H, 5.17; N, 14.75. Found: C, 72.38; H, 4.87; N, 14.66.

### Example 20

Preparation of 1-N,N-Dimethylcarbamoyl-3-{3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

20 The desired compound was prepared according to the method of Example 2, except substituting 3-{3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole, prepared as in Example 19, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. mp 134-136 °C. <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.63 (s, 3H), 3.02 (s, 6H), 5.70 (s, 2H), 7.32-7.44 (c, 3H), 7.52-7.58 (c, 2H), 7.64 (d, 1H, J = 4.5 Hz), 7.68 (s, 1H), 7.79 (d, 1H, J = 4.5 Hz), 8.01 (s, 1H), 8.24 (d, 1H, J = 4.5 Hz), 8.29 (d, 1H, J = 3.0 Hz), 8.86 (s, 1H). IR (KBr) 1700, 1630, 1610, 1580, 1530, 1505, 1450, 1390, 1310, 1230, 1190, 1180, 1080, 830, 780  $\text{cm}^{-1}$ . MS (DCI/ $\text{NH}_3$ )  $m/e$  438 ( $\text{M}+\text{H}$ )<sup>+</sup>. Anal calcd for  $\text{C}_{26}\text{H}_{26}\text{FN}_5\text{O}_{3.5}$ : C, 67.22; H, 5.64; N, 15.08. Found: C, 67.25; H, 5.25; N, 14.89.

### Example 21

Preparation of 3-{4-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)]benzoyl}indole.

The desired compound was prepared according to the method of Example 9, except preparing the indolylzinc reagent from indole instead of 6-(4-fluorophenyl)indole. mp 239.5-240.5 °C. <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.58 (s, 3H), 7.26-7.32 (c, 2H), 7.34 (dd, 1H, J = 1, 6 Hz), 7.53-7.58 (c, 1H), 7.72-

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7.80 (c, 2H), 8.01-8.07 (c, 2H), 8.07-8.11 (c, 1H), 8.29-8.93 (c, 1H), 8.95 (d, 1H,  $J = 6$  Hz), 8.95 (s, 1H), 12.17 (bs, 1H). IR (KBr) 3160, 1600, 1575, 1565, 1510, 1490, 1430, 1380, 1210, 895  $\text{cm}^{-1}$ . MS (DCI/ $\text{NH}_3$ )  $m/e$  353 ( $\text{M}+\text{H}$ )<sup>+</sup>, 281, 253, 130, 118.

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**Example 22**

Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)]benzoyl}indole, prepared as in Example 21, for 6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}indole. mp 241.1-241.7 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.58 (s, 3H), 3.06 (s, 6H), 7.35 (dd, 1H,  $J = 1.5, 6\text{Hz}$ ), 7.39-7.45 (c, 2H), 7.64-7.69 (c, 1H), 7.76-7.83 (c, 2H), 8.08-8.14 (c, 2H), 8.28 (s, 1H), 8.32-8.39 (c, 2H), 8.96 (bs, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  424 ( $\text{M}+\text{H}$ )<sup>+</sup>.

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**Example 23**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methylcarbonyl]indole.

Step 1: 1-Chloro-2-[6-(4-fluorophenyl)indol-3-yl]ethanone.

A solution under  $\text{N}_2$  of 6-(4-fluorophenyl)indole (10.0 g, 47.4 mmol), prepared as described in WO 93/01813, in dioxane (36 mL) and pyridine (5.8 mL, 71.8 mmol) was heated to 60 °C and a solution of chloroacetyl chloride (5.7 mL, 71.1 mmol) in dioxane (12.5 mL) was added dropwise over 1 hour. The reaction mixture was stirred for 1 hour at 60 °C, then cooled to ambient temperature and poured into a mixture of  $\text{H}_2\text{O}$  (200 mL) and ether (50 mL). The resulting orange precipitate was filtered and dried. Recrystallization from ethanol, followed by rinsing with cold ether gave 1-chloro-2-[6-(4-fluorophenyl)indol-3-yl]ethanone (2.8 g) as an orange solid.

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Step 2: 1-Chloro-2-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-yl]ethanone.

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The desired compound was prepared according to the method of Example 2, except substituting 1-chloro-2-[6-(4-fluorophenyl)indol-3-yl]ethanone, prepared as in step 1, for 6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}indole.

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Step 3: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole

To a solution under N<sub>2</sub> of 1H-2-methylimidazo[4,5-c]pyridine (372 mg, 2.80 mmol), prepared as in Example 3, step 1, in a mixture of THF (13.2 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinole (DMPU, 4.4 mL) was added NaH (81 mg, 3.36 mmol) and the resulting yellow suspension was stirred for 50 min at ambient temperature. In a separate flask, a mixture of 1-chloro-2-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-yl]ethanone (1.00 g, 2.80 mmol), prepared as in step 2, and NaBr (577 mg, 5.60 mmol) in THF (13.2 mL) was cooled to 0 °C. The imidazopyridine/NaH suspension was then added via syringe, and the orange solution was warmed slowly to ambient temperature and stirred for 17 hours. The reaction mixture was partitioned between H<sub>2</sub>O (75 mL) and ethyl acetate (75 mL). The layers were separated and the aqueous phase was washed with ethyl acetate (2x75 mL), and the combined organic extracts were washed with H<sub>2</sub>O (2x75 mL). The combined aqueous extracts were extracted twice with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (8% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole (92.6 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.54 (s, 3H), 3.15 (s, 6H), 5.99 (s, 2H), 7.25-7.35 (m, 2H), 7.58 (d, 1H, J = 5.4 Hz), 7.64 (dd, 1H, J = 8.1, 1.2 Hz), 7.7-7.8 (m, 2H), 7.87 (s, 1H), 8.19 (d, 1H, J = 8.1 Hz), 8.30 (d, 1H, J = 5.4 Hz), 8.84 (s, 1H), 8.95 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 456 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>22</sub>FN<sub>5</sub>O<sub>2</sub> · 1.7H<sub>2</sub>O: C, 64.24; H, 5.27; N, 14.41. Found: C, 64.58; H, 5.20; N, 13.81.

**Example 24**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole.

The desired compound (58.3 mg) was obtained from the chromatography described in Example 23. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.15 (s, 6H), 5.93 (s, 2H), 7.25-7.35 (m, 2H), 7.56 (d, 1H, J = 5.4 Hz), 7.63 (d, 1H, J = 9.3 Hz), 7.7-7.8 (m, 2H), 7.89 (s, 1H), 8.19 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, 5.7 Hz), 8.86 (s, 1H), 8.95 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 456 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>22</sub>FN<sub>5</sub>O<sub>2</sub> · 2H<sub>2</sub>O: C, 63.53; H, 5.33; N, 14.25. Found: C, 63.62; H, 5.04; N, 13.93.

**Example 25**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole.

The desired compound was prepared according to the method of Example 23, except substituting indole for 6-(4-fluorophenyl)indole and separating the isomers by chromatography on silica gel using 5% methanol/CH<sub>2</sub>Cl<sub>2</sub> instead of 8% methanol/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.12 (s, 6H), 5.97 (s, 2H), 7.3-7.45 (m, 2H), 7.55-7.60 (m, 1H), 7.65-7.70 (m, 1H), 8.14 (d, 1H, J = 7.8 Hz), 8.29 (dd, 1H, J = 5.4, 1.2 Hz), 8.23 (s, 1H), 8.92 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 362 (M+H)<sup>+</sup>.

**Example 26**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole.

The desired compound was obtained in the chromatography described in Example 25. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz) δ 2.52 (s, 3H), 3.12 (s, 6H), 5.90 (s, 2H), 7.30-7.45 (m, 2H), 7.54 (dd, 1H, J = 5.4, 1.2 Hz), 7.67 (d, 1H, 8.1 Hz), 8.14 (d, 1H, J = 7.2 Hz), 8.27 (d, 1H, J = 5.4 Hz), 8.85 (s, 1H), 8.91 (s, 1H). MS (FAB) m/e 362 (M+1)<sup>+</sup>. Anal calcd for C<sub>20</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub> · 1.1H<sub>2</sub>O: C, 63.01; H, 5.61; N, 18.37. Found: C, 63.25; H, 5.61; N, 18.03.

**Example 27**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[(3H-2-methylimidazo[4.5-b]pyrid-3-yl)methyl]benzoyl}indole.Step 1: 1H-2-Methylimidazo[4.5-b]pyridine.

A solution of 2,3-diaminopyridine (10.0 g, 91.7 mmol) in acetic anhydride (83.4 mL, 888 mmol) was heated at 140 °C for 18.5 hours. The black solution was then cooled to ambient temperature and stirred for 17 hours. The reaction mixture was cooled in an ice bath and a solution of NaOH (70.8 g, 1.77 mol) in H<sub>2</sub>O (200 mL) was added dropwise to bring the reaction to pH 9. The reaction mixture was poured into ethyl acetate (200 mL) and the layers were separated. The organic phase was washed with H<sub>2</sub>O (2x100 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The aqueous phase was transferred to a continuous extraction vessel and extracted with ethyl acetate for 17 hours. The resulting ethyl acetate solution was combined with the product from above and concentrated *in vacuo*. Chromatography



on silica gel (10% methanol/CH<sub>2</sub>Cl<sub>2</sub> gave 5.07 g of 1H-2-methylimidazo[4,5-b]pyridine.

Step 2: Methyl 4-(3H-2-methylimidazo[4,5-b]pyrid-3-ylmethyl)benzoate.

5 To a solution under N<sub>2</sub> of 1H-2-methylimidazo[4,5-b]pyridine (3.00 g, 22.6 mmol), prepared as in step 1, in THF (113 mL) and DMF (25 mL) was added NaH (758 mg, 31.6 mmol). The resulting suspension was stirred for 1 hour at ambient temperature, then cooled to 0 °C and a solution of methyl (4-bromomethyl)benzoate (6.20 g, 27.1 mmol) in THF (30 mL) was added via cannula. The cold bath was  
10 removed and the reaction mixture was stirred for 70 hours at ambient temperature. The reaction mixture was partitioned between H<sub>2</sub>O (100 mL) and ethyl acetate (200 mL). The organic phase was extracted with H<sub>2</sub>O (75 mL), and the combined aqueous phases were extracted with ethyl acetate (3x150 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on  
15 silica gel (2%, then 5%, then 7% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave methyl 4-(3H-2-methylimidazo[4,5-b]pyrid-3-ylmethyl)benzoate (2.89 g), methyl 4-(1H-2-methylimidazo[4,5-b]pyrid-1-ylmethyl)benzoate (1.36 g), and methyl 4-(4H-2-methylimidazo[4,5-b]pyrid-4-ylmethyl)benzoate (1.16 g).

20 Step 3: 3-{4-[(3H-2-Methylimidazo[4.5-b]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 15, except substituting methyl 3-(3H-2-methylimidazo[4,5-b]pyrid-3-ylmethyl)benzoate, prepared as in step 2, for methyl 4-(5H-2-methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoate.

25

Step 4: 1-N,N-Dimethylcarbamoyl-3-{4-[(3H-2-methylimidazo[4.5-b]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 3-{4-[(3H-2-methylimidazo[4.5-b]pyrid-1-yl)methyl]benzoyl}indole, prepared as in step 3, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ  
30 2.57 (s, 3H), 3.00 (s, 6H), 5.63 (s, 2H), 7.28 (dd, 1H, J = 8.1, 5.1 Hz), 7.3-7.4 (m, 4H), 7.6-7.7 (m, 1H), 7.83 (apparent d, 2H, J = 7.8 Hz), 8.00 (dd, 1H, J = 7.8, 1.2 Hz), 8.11 (s, 1H), 8.2-8.3 (m, 1H), 8.30-8.35 (m, 1H). MS (DCI/NH<sub>3</sub>) m/e  
35 438 (M+H)<sup>+</sup>.

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**Example 28**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4,5-*b*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 27, except substituting methyl 4-(1*H*-2-methylimidazo[4,5-*b*]pyrid-1-ylmethyl)benzoate, prepared as in Example 27, step 2, for methyl 4-(3*H*-2-methylimidazo[4,5-*b*]pyrid-3-ylmethyl)benzoate. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.61 (s, 3H), 3.00 (s, 6H), 5.66 (s, 2H), 7.22 (dd, 1H, *J* = 8.1, 4.8 Hz), 7.30-7.45 (m, 4H), 7.63 (d, 1H, *J* = 8.1 Hz), 7.84 (apparent d, 2H, *J* = 8.1 Hz), 7.98 (d, 1H, *J* = 8.1 Hz), 8.10 (s, 1H), 8.25-8.30 (m, 1H), 8.35-8.40 (m, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 438 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub> · 1.9H<sub>2</sub>O: C, 66.20; H, 5.73; N, 14.85. Found: C, 66.49; H, 5.46; N, 14.34.

**Example 29**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[1*H*-2-trifluoromethylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.Step 1: 4-(*N-tert*-Butoxycarbonylaminomethyl)benzoic acid.

To a solution of 4-aminomethylbenzoic acid (11.1 g, 73.4 mmol) in 1*N* aqueous NaOH (100 mL) was added THF (100 mL) and di-*tert*-butyldicarbonate (16.8 g, 77.1 mmol). The reaction mixture was stirred for 2 hours at ambient temperature, then acidified to pH 2 and extracted 3 times with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 4-(*N-tert*-butoxycarbonylaminomethyl)benzoic acid (18.3 g) as white crystals which was used without further purification.

Step 2: 3-[4-(*N-tert*-Butoxycarbonylaminomethyl)benzoyl]indole.

To a 0 °C solution of 4-(*N-tert*-butoxycarbonylaminomethyl)benzoic acid (5.07 g, 20.2 mmol) in CHCl<sub>3</sub> was added DMF (200  $\mu$ L) and oxalyl chloride (1.94 mL, 22.2 mmol). The cold bath was removed and the reaction mixture was stirred for 2 hours at ambient temperature, after which it was concentrated *in vacuo*. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and added to a solution of indolylzinc (50.5 mmol, prepared as described in Example 1, step 4, except substituting indole for 6-(4-fluorophenyl)indole). The reaction mixture was stirred for 16 hours at ambient temperature, then quenched with saturated aqueous NH<sub>4</sub>Cl and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NH<sub>4</sub>Cl. The solids were filtered off and rinsed with CH<sub>2</sub>Cl<sub>2</sub>. The layers were separated and the organic phase was dried over MgSO<sub>4</sub>.

filtered, and concentrated *in vacuo*. Pure 3-[4-(*N*-*tert*-butoxycarbonylaminomethyl)benzoyl]indole (3.10 g) was obtained by chromatography on silica gel (60% ether/hexanes, then 60% ethyl acetate/hexanes).

5    Step 3: 1-*N,N*-Dimethylcarbamoyl-3-[4-(*N*-*tert*-butoxycarbonylaminomethyl)-benzoyl]indole.

Sodium hydride (60% dispersion in mineral oil, 251 mg, 6.29 mmol) was washed twice with hexanes and added to a solution of 3-[4-(*N*-*tert*-butoxycarbonylaminomethyl)benzoyl]indole (1.00g, 2.86 mmol), prepared as in step  
10    2, in THF (40 mL). After stirring for 10 min, dimethylcarbamoyl chloride (315  $\mu$ L, 3.43 mmol) was added and the reaction mixture was stirred for 10 min. The reaction mixture was poured into saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with ethyl acetate. The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Chromatography on silica gel gave 1-*N,N*-  
15    dimethylcarbamoyl-3-[4-(*N*-*tert*-butoxycarbonylaminomethyl)benzoyl]indole (870 mg, 72%).

Step 4: 1-*N,N*-Dimethylcarbamoyl-3-(4-aminomethylbenzoyl)indole.

To a solution of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-*tert*-butoxycarbonylaminomethyl)benzoyl]indole (870 mg, 2.07 mmol), prepared as in  
20    step 3, in ethyl acetate (10 mL) was added 3N aqueous HCl (2 mL). The reaction mixture was stirred for 17 hours at ambient temperature, and an additional 4 mL of 3N aqueous HCl was added. The reaction mixture was stirred for a further 10 hours and then was adjusted to pH 1 and extracted three times with ethyl acetate. The combined  
25    organic extracts were washed with  $\text{H}_2\text{O}$ , and the aqueous layers were combined, adjusted to pH 12, and extracted three times with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extracts were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give 620 mg of 1-*N,N*-dimethylcarbamoyl-3-(4-aminomethylbenzoyl)indole which was used without  
30    further purification.

Step 5: 1-*N,N*-Dimethylcarbamoyl-3-[4-(*N*-3-nitropyridin-4-yl)aminomethyl-benzoyl]indole.

To a solution of 1-*N,N*-dimethylcarbamoyl-3-(4-aminomethylbenzoyl)indole (0.620g, 1.93 mmol), prepared as in step 4, in THF (10 mL) was added triethylamine  
35    (403  $\mu$ L, 2.90 mmol) and 3-nitro-4-chloropyridine (0.300g, 1.93 mmol), prepared as described by Wright, G. C., *J. Heterocyclic Chem.* **1976**, *13*, 601, and Kruger, S.

and Mann, F.G., *J. Chem. Soc.* 2 **1955**, 758. The reaction mixture was heated for 17 hours at 45 °C, then additional 3-nitro-4-chloropyridine (40 mg) was added and heating was continued for 2 hours at which all to the starting material was consumed. The reaction mixture was poured into a mixture of saturated aqueous NH<sub>4</sub>Cl and brine and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (60% ethyl acetate/hexanes, then 10% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl]indole (903 mg).

Step 6: 1-*N,N*-Dimethylcarbamoyl-3-[4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl]indole.

A mixture of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl]indole (141 mg), prepared as in step 5, and 10% palladium on activated carbon (40 mg) in 5:1 ethanol/CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred under 1 atmosphere of hydrogen for 4 hours. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to give 131 mg of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl]indole which was used without further purification.

Step 7: 1-*N,N*-Dimethylcarbamoyl-3-{4-[1H-2-trifluoromethylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

A mixture of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl]indole (131 mg), prepared as in step 6, trifluoroacetic anhydride (1.0 mL), and trifluoroacetic acid (0.5 mL) was heated at 45 °C for 17 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. Chromatography on silica gel (ethyl acetate) gave 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-trifluoromethylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (107 mg, 68% yield for steps 4 and 5). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.99 (s, 6H), 5.89 (s, 2H), 7.30 (d, 2H, J = 8.7 Hz), 7.32-7.42 (m, 2H), 7.61-7.63 (m, 1H), 7.84 (d, 2H, J = 8.7 Hz), 7.85-7.88 (m, 1H), 8.08 (s, 1H), 8.23-8.26 (m, 1H), 8.58 (d, 1H, J = 6 Hz). MS (DCI/NH<sub>3</sub>) m/e 492 (M+H)<sup>+</sup>, 409, 306. Anal calcd for C<sub>26</sub>H<sub>20</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub> · 1.25 CF<sub>3</sub>CO<sub>2</sub>H: C, 53.99; H, 3.37; N, 11.04. Found: C, 53.76; H, 3.55; N, 11.10.

**Example 30**Preparation of 1-*N,N*-Dimethylcarbamoyl-6-3-{4-[1H-imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl]indole (44.9 mg, 0.11 mmol), prepared as in Example 29, step 5, in acetic acid (1.5 mL) was added ethyl (ethoxymethylene)cyanoacetate (27.6 mg, 0.16 mmol). The reaction mixture was heated at 90 °C for 4 hours, then cooled to ambient temperature and concentrated *in vacuo*. 1-*N,N*-dimethylcarbamoyl-6-3-{4-[1H-imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (15.6 mg) was isolated by thin layer chromatography (10% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 9.19 (s, 1H), 8.47 (d, 1H, J = 5.7 Hz), 8.38 (m, 1H), 8.11 (s, 1H), 7.86 (2H, d, J = 8.4 Hz), 7.73 (s, 1H), 7.53 (m, 1H), 7.40 (m, 2H), 7.31 (m, 3H), 5.49 (s, 2H), 3.08 (s, 6H). MS (DCI/NH<sub>3</sub>) m/e 424 (M+H)<sup>+</sup>, 306, 120.

**Example 31**Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[1H-2-(2-propyl)imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.Step 1: 1-*N,N*-Dimethylcarbamoyl-3-[4-(*N*-3-(2-propyl)aminopyridin-4-yl)-*N*-(2-propyl)aminomethylbenzoyl]indole.

The desired compound (66.4 mg) was prepared according to the method of Example 29, step 6, except substituting isobutyric anhydride and isobutyric acid for trifluoroacetic anhydride and trifluoroacetic acid.

Step 2: 1-*N,N*-Dimethylcarbamoyl-3-{4-[1H-2-(2-propyl)imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole-1-carboxylic acid dimethylamide.

A solution of 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-(2-propyl)aminopyridin-4-yl)-*N*-(2-propyl)aminomethylbenzoyl]indole (62.5 mg) in trifluoroacetic acid (1.0 mL) was heated at 70 °C for 17 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-(2-propyl)imidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (50.6 mg) was obtained by thin layer chromatography (7% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.31 (d, 6H, J = 6.8 Hz), 3.01 (s, 6H), 3.47 (m, 1H), 5.92 (2H, s), 7.31 (d, 2H, J = 8.4 Hz), 7.32-7.42 (m, 2H), 7.62 (d, 1H, J = 7.5 Hz), 7.86 (d, 2H, J = 8.4 Hz), 8.04 (s, 1H), 8.23 (d, 1H, J = 7.5 Hz), 8.29 (d, 1H, J = 6.4 Hz), 8.69 (d, 1H, J = 6.4 Hz), 9.49 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 466 (M+H)<sup>+</sup>, 162. Anal calcd for

$C_{28}H_{27}N_5O_2 \cdot 2.25H_2O$ : C, 66.45; H, 6.24; N, 12.73. Found: C, 66.80; H, 6.27; N, 13.84.

### Example 32

#### Preparation of 1-N,N-Dimethylcarbamoyl-3-{4-[1H-2-phenylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution of 1-N,N-dimethylcarbamoyl-3-[4-(N-3-aminopyridin-4-yl)aminomethylbenzoyl]indole (38 mg), prepared as in Example 29, step 5, in  $CH_2Cl_2$  was added triethylamine and benzoyl chloride. The reaction mixture was stirred for 20 hours at ambient temperature and was then partitioned between  $CH_2Cl_2$  and saturated aqueous  $NaHCO_3$ . The organic phase was dried over  $MgSO_4$ , filtered, and concentrated *in vacuo*. Pure 1-N,N-dimethylcarbamoyl-3-{4-[1H-2-phenylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (21 mg, 41%) was obtained by thin layer chromatography (10% methanol/ $CH_2Cl_2$ ).  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  3.09 (s, 6H), 5.58 (s, 2H), 7.20 (d, 2H, J = 8.5 Hz), 7.24 (d, 1H, J = 6 Hz), 7.36-7.44 (m, 2H), 7.50-7.58 (m, 4H), 7.71 (dd, 2H, J = 7.8, 2.2 Hz), 7.79 (s, 1H), 7.85 (d, 2H, J = 8.5 Hz), 8.38-8.41 (m, 1H), 8.46 (d, 1H, J = 5.4 Hz), 9.21 (s, 1H). MS (DCI/ $NH_3$ ) m/e 500 (M+H)<sup>+</sup>, 318.

### Example 33

#### Preparation of 1-N,N-Dimethylcarbamoyl-3-{4-[1H-2-ethylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound (66.4 mg) was prepared according to the method of Example 29, step 6, except substituting propionic anhydride and propionic acid for trifluoroacetic anhydride and trifluoroacetic acid.  $^1H$  NMR ( $DMSO-d_6$ , 300 MHz)  $\delta$  1.32 (t, 3H, J = 7.5 Hz), 2.91 (q, 2H, J = 7.5 Hz), 2.99 (s, 6H), 5.66 (s, 2H), 7.28 (d, 2H, J = 8.1 Hz), 7.32-7.42 (m, 2H), 7.62 (d, 2H, J = 6 Hz), 7.83 (d, 2H, J = 8.1 Hz), 8.09 (s, 1H), 8.25 (dd, 1H, J = 6.3, 2.1 Hz), 8.31 (d, 1H, J = 6.3 Hz), 8.91 (s, 1H). MS (DCI/ $NH_3$ ) m/e 452 (M+H)<sup>+</sup>, 306. Anal calcd for  $C_{27}H_{25}N_5O_2 \cdot 1H_2O$ : C, 69.06; H, 5.79; N, 14.91. Found: C, 69.07; H, 5.71; N, 14.76.

### Example 34

#### Preparation of 1-N,N-Dimethylcarbamoyl-3-{3-[(5H-2-methylimidazo[4.5-c]pyrid-5-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 17, except substituting methyl 3-(5H-2-methylimidazo[4,5-c]pyrid-5-ylmethyl)benzoate, prepared as in Example 11, step 1, for methyl 3-(1H-2-methylimidazo[4,5-c]pyrid-1-

60

ylmethyl)benzoate. mp 230-232 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.50 (s, 3H), 5.75 (s, 2H), 7.20-7.30 (c, 2H), 7.50-7.60 (c, 4H), 7.76 (d, 1H, J = 4.5 Hz), 7.88 (s, 1H), 7.91(d, 1H, J = 1.5 Hz), 8.20-8.23 (c, 2H), 9.00(s, 1H), 12.10 (bs,1H). IR (KBr) 1630, 1580, 1530, 1500, 1445, 1370, 1320, 1235, 1180, 1150  
5 cm<sup>-1</sup>. MS (DCI/NH<sub>3</sub>) m/e 367 (M+H)<sup>+</sup>, 134, 118.

### Example 35

Preparation of 1-N,N-Dimethylcarbamoyl-3-{3-[(5H-2-methylimidazo[4.5-c]pyrid-5-yl)methyl]benzoyl}indole.

10 The desired compound was prepared according to the method of Example 2, except substituting 3-{3-[(5H-2-methylimidazo[4.5-c]pyrid-5-yl)methyl]benzoyl}indole, prepared as in Example 34, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. mp 194.4-196.4 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 3.01 (s, 6H), 5.74 (s, 2H), 7.38 (dm, 2H, J = 7.5, 1.5  
15 Hz), 7.55-7.62 (c, 2H), 7.62-7.71 (c, 2H), 7.83 (dt, 1H, J = 1, 7.5 Hz), 7.92 (bs, 1H), 8.07 (s, 1H), 8.19-8.28 (c, 2H), 9.00 (bs, 1H). IR (KBr) 1690, 1630, 1600, 1580, 1530, 1470, 1450, 1390, 1310, 1230, 1190, 1170, 1120, 1080 cm<sup>-1</sup>. MS (DCI/NH<sub>3</sub>) m/e 438 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>28</sub>N<sub>5</sub>O<sub>4.5</sub>: C, 64.71; H, 5.85; N, 14.52. Found: C, 64.59; H, 5.45; N, 14.30.

20

### Example 36

Preparation of 1-N,N-dDimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)pent-5-ylcarbonyl]indole.

Step 1: 6-Bromo-1-[6-(4-fluorophenyl)-1-N,N-dimethylcarbamoylindol-3-yl]hexanone.

25 To a solution of 6-bromohexanoyl chloride (596 μL, 3.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added AlCl<sub>3</sub> (1.00g, 7.8 mmol) in a single portion and the reaction mixture was stirred for 1 hour at ambient temperature. A solution of 6-(4-fluorophenyl)-1-N,N-dimethylcarbamoylindole (1.00 g, 3.55 mmol), prepared as in Example 4, step 1, in  
30 CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise and the solution was stirred for 1 hour at ambient temperature. The reaction mixture was partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>. The layers were separated and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography  
35 on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) gave 6-chloro-1-[6-(4-fluorophenyl)-1-N,N-dimethylcarbamoylindol-3-yl]hexanone (1.57 g) as an off-white solid.

Step 2: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)pent-5-ylcarbonyl]indole.

The desired compounds were prepared according to the method of Example 23, step 2, except substituting 6-chloro-1-[6-(4-fluorophenyl)-1-*N,N*-dimethylcarbamoylindol-3-yl]hexanone, prepared as in step 1, for 1-chloro-2-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-yl]ethanone. Chromatography on silica gel (2%, then 3%, then 4%, then 15% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)pent-5-ylcarbonyl]indole (137 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.35-1.45 (m, 2H), 1.65-1.75 (m, 2H), 1.75-1.85 (m, 2H), 2.59 (s, 3H), 2.92 (t, 2H, J = 7.4 Hz), 3.07 (s, 6H), 4.29 (t, 2H, J = 7.4 Hz), 7.25-7.35 (m, 2H), 7.50 (dd, 1H, J = 5.4, 1.0 Hz), 7.59 (dd, 1H, J = 8.4, 1.8 Hz), 7.7-7.8 (m, 4H), 8.25-8.35 (m, 2H), 8.58 (d, 1H, J = 1.0 Hz). MS (DCI/NH<sub>3</sub>) m/e 512 (M+H)<sup>+</sup>.

15

### Example 37

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)pent-5-ylcarbonyl]indole.

The desired compound (184 mg) was obtained from the chromatography described in Example 36, step 2. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.30-1.45 (m, 2H), 1.65-1.85 (m, 4H), 2.58 (s, 3H), 2.91 (t, 2H, J = 7.4 Hz), 3.06 (s, 6H), 4.22 (t, 2H, J = 7.4 Hz), 7.25-7.35 (m, 2H), 7.5-7.6 (m, 2H), 7.7-7.8 (m, 3H), 8.2-8.3 (m, 2H), 8.58 (s, 1H), 8.78 (d, 1H, J = 1.0 Hz). MS (DCI/NH<sub>3</sub>) m/e 512 (M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>30</sub>FN<sub>5</sub>O<sub>2</sub> · 0.8H<sub>2</sub>O: C, 68.50; H, 6.05; N, 13.31. Found: C, 68.52; H, 5.99; N, 13.26.

25

### Example 38

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(5H-2-methylimidazo[4.5-c]pyrid-5-yl)pent-5-ylcarbonyl]indole.

The desired compound (431 mg) was obtained in the chromatography described in Example 36, step 2. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.3-1.4 (m, 2H), 1.65-1.75 (m, 2H), 1.9-2.0 (m, 2H), 2.51 (s, 1H), 2.93 (t, 2H, J = 7.4 Hz), 3.07 (s, 6H), 4.42 (t, 2H, 7.1 Hz), 7.2-7.3 (m, 2H), 7.5-7.6 (m, 2H), 7.7-7.8 (m, 3H), 8.05 (dd, 1H, J = 6.7, 1.3 Hz), 8.28 (d, 1H, J = 8.4 Hz), 8.58 (s, 1H), 8.78 (d, 1H, J = 1.3 Hz). MS (DCI/NH<sub>3</sub>) m/e 512 (M+H)<sup>+</sup>.

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**Example 39****Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.**

The desired compound was prepared according to the method of Example 4, except substituting 6-(4-fluorophenoxy)indole for 6-(4-fluorophenyl)indole. Chromatography on silica gel (2%, then 3%, then 4% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.62 (s, 3H), 2.97 (s, 6H), 5.72 (s, 2H), 7.05-7.15 (m, 3H), 7.2-7.3 (m, 3H), 7.35 (apparent d, 2H, J = 8.4 Hz), 7.59 (dd, 1H, J = 5.4, 1.2 Hz), 7.85 (apparent d, 2H, J = 8.4 Hz), 8.08 (s, 1H), 8.23 (d, 1H, J = 8.7 Hz), 8.31 (d, 1H, J = 5.7 Hz), 8.90 (d, 1H, 1.2 Hz). MS (DCI/NH<sub>3</sub>) m/e 548 (M+H)<sup>+</sup>.

**Example 40****Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.**

The desired compound was obtained in the chromatography described in Example 39. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 2.97 (s, 6H), 5.66 (s, 2H), 7.05-7.10 (m, 3H), 7.2-7.3 (m, 3H), 7.30 (apparent d, 2H, J = 8.4 Hz), 7.63 (dd, 1H, J = 5.7, 1.0 Hz), 7.84 (apparent d, 2H, J = 8.4 Hz), 8.08 (s, 1H), 8.23 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 5.7 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 548 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub>F: C, 67.52; H, 5.03; N, 12.30. Found: C, 67.57; H, 4.79; N, 12.01.

**Example 41****Preparation of 1-*N,N*-Dimethylcarbamoyl-6-phenylmethyl-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.**

The desired compound was prepared according to the method of Example 4, except substituting 6-phenylmethylindole for 6-(4-fluorophenyl)indole. 1-*N,N*-dimethylcarbamoyl-6-phenylmethyl-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole was isolated by chromatography on silica gel (3%, then 4%, then 5% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.62 (s, 3H), 2.98 (s, 6H), 4.08 (s, 2H), 5.71 (s, 2H), 7.1-7.3 (m, 6H), 7.33 (apparent d, 2H, J = 7.8 Hz), 7.49 (s, 1H), 7.58 (dd, 1H, J = 5.4, 1.0 Hz), 7.83 (apparent d, 2H, J = 8.7 Hz), 8.04 (s, 1H), 8.14 (d, 1H, J = 8.1 Hz), 8.31 (d, 1H, J = 5.4 Hz), 8.88 (d, 1H, J = 1.0 Hz). MS (DCI/NH<sub>3</sub>) m/e 528 (M+H)<sup>+</sup>.

**Example 42**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-phenylmethyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was isolated in the chromatography described in  
5 Example 41. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.58 (s, 3H), 2.98 (s, 6H), 4.08 (s, 2H), 5.65 (s, 2H), 7.15-7.30 (m, 8H), 7.49 (s, 1H), 7.62 (dd, 1H, *J* = 5.4, 1.2 Hz), 7.82 (apparent d, 2H, *J* = 8.1 Hz), 8.03 (s, 1H), 8.14 (d, 1H, *J* = 8.1 Hz), 8.31 (d, 1H, *J* = 5.4 Hz), 8.86 (d, 1H, *J* = 1.0 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 528 (M+H)<sup>+</sup>.

**Example 43**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole.

Step 1: 4-methoxycarbonylindole.

To a 0 °C solution of indole-4-carboxylic acid (1.00g, 6.21 mmol) in ether (60  
15 mL) was added diazomethane (0.3M solution in ether, 24.8 mL, 7.45 mmol) and the reaction mixture was stirred for 0.5 hours at 0 °C. An additional 20 mL of diazomethane solution was then added and stirring was continued for 1 hour at 0 °C. The reaction mixture was quenched with formic acid (1.0 mL) and concentrated *in vacuo* to give 4-methoxycarbonylindole (1.1 g) as an off white powder.

20

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 4, except substituting 4-methoxycarbonylindole, prepared as in step 1, for 6-(4-  
25 fluorophenylindole). 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole was isolated by chromatography on silica gel (3%, then 5%, then 6% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.70 (s, 2H), 7.32 (apparent d, 2H, *J* = 8.1 Hz), 7.4-7.5 (m, 1H), 7.56 (dd, 1H, *J* = 2.1, 1.0 Hz), 7.56-7.58 (m, 1H), 7.85 (apparent d, 2H, *J* = 8.1 Hz), 7.86 (dd, 1H, *J* = 8.1, 1.2 Hz), 8.11 (s, 1H), 8.30 (d, 1H, *J* = 5.7 Hz), 8.86 (d, 1H, *J* = 1.0 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 496 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> · 1.8 H<sub>2</sub>O: C, 63.70; H, 5.46; N, 13.26. Found: C, 63.68; H, 5.12; N, 12.95.

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**Example 44**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

- The desired compound was isolated in the chromatography described in
- 5 Example 43. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.64 (s, 2H), 7.28 (apparent d, 2H, *J* = 8.4 Hz), 7.4-7.5 (m, 1H), 7.55-7.60 (m, 2H), 7.84 (apparent d, 2H, *J* = 8.4 Hz), 7.86 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.10 (s, 1H), 8.30 (d, 1H, *J* = 5.7 Hz), 8.86 (d, 1H, *J* = 1.0 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 496 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> · 1.9 H<sub>2</sub>O: C, 63.48; H, 5.48; N, 13.22.
- 10 Found: C, 63.69; H, 5.08; N, 12.73.

**Example 45**

Preparation of 1-*N,N*-Dimethylcarbamoyl-5-phenylmethoxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

- 15 The desired compound is prepared according to the method of Example 4, except substituting 5-benzyloxyindole for 6-(4-fluorophenyl)indole.

**Example 46**

- Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-methoxyphenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.
- 20

The desired compound is prepared according to the method of Example 4, except substituting 6-(4-methoxyphenyl)indole, prepared as described in WO 93/01813, for 6-(4-fluorophenyl)indole.

25

**Example 47**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(pyrid-3-yl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

- The desired compound is prepared according to the method of Example 4, except substituting 6-(pyrid-3-yl)indole, prepared as described in WO 93/01813, for
- 30 6-(4-fluorophenyl)indole.

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**Example 48**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-bromo-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

5 The desired compound is prepared according to the method of Example 4, except substituting 6-bromoindole for 6-(4-fluorophenyl)indole.

**Example 49**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-chloro-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

10 The desired compound is prepared according to the method of Example 4, except substituting 6-chloroindole for 6-(4-fluorophenyl)indole.

**Example 50**

15 Preparation of 1-*N,N*-Dimethylcarbamoyl-5-methoxy-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound is prepared according to the method of Example 4, except substituting 5-methoxyindole for 6-(4-fluorophenyl)indole.

**Example 51**

20 Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]thien-2-oyl}indole.

Step 1: 5-Methyl-2-carboxymethylthiophene.

25 The desired compound was prepared according to the method of Example 43, step 1, except substituting 5-methyl-2-thiophenecarboxylic acid for indole-4-carboxylic acid.

Step 2: 5-Bromomethyl-2-carboxymethylthiophene.

30 To a solution of *N*-bromosuccinimide (5.94 g, 33 mmol) in hexanes (16 mL) was added 5-methyl-2-carboxymethylthiophene (5.0 g, 32 mmol), prepared as in step 1, followed by 1 drop of perchloric acid. The reaction mixture was stirred for 22 hours at ambient temperature and then partitioned between ethyl acetate and saturated aqueous  $\text{NaHSO}_3$  solution. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give 6.17 g of 5-bromomethyl-2-carboxymethylthiophene as a yellow oil.

35

Step 3: 5-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-carboxymethylthiophene.

To a solution of 1H-2-methylimidazo[4.5-c]pyridine (2.00 g, 15 mmol), prepared as in Example 3, step 1, in DMSO (150 mL) was added potassium *tert*-butoxide (1.7 g, 17 mmol) and the reaction mixture was stirred until all of the base dissolved (~15 min). After a further 5 min, 5-bromomethyl-2-carboxymethylthiophene (4.0 g, 17 mmol), prepared as in step 2, was added. The reaction mixture was stirred for 2 hours at ambient temperature and then partitioned between ethyl acetate (2 L), and 1:1 pH 7 buffer/brine (1 L). The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (3%, then 4%, then 5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-carboxymethylthiophene.

Step 4: 5-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-thiophenecarboxylic acid.

To a solution of 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-carboxymethylthiophene (0.360 g, 1.25 mmol) in THF (15 mL) and H<sub>2</sub>O (2 mL) was added lithium hydroxide hydrate (0.114 g, 2.70 mmol). The reaction mixture was stirred for 6 hours at ambient temperature and then quenched with 4N HCl/dioxane (1 mL) and partitioned between ethyl acetate and H<sub>2</sub>O. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-thiophenecarboxylic acid (0.46 g) as an oil.

Step 5: 6-(4-Fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thien-2-oyl}indole.

The desired compound was prepared according to the method of Example 1, step 4, except substituting 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-thiophenecarboxylic acid, prepared as in step 4, for 4-(1H-2-methylbenzimidazol-1-ylmethyl)benzoic acid.

Step 6: 1-N,N-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thien-2-oyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thien-2-oyl}indole, prepared as in step 5, for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole. mp 200-203 C. <sup>1</sup>H NMR

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(CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.06 (s, 1H), 8.44 (d, 1H, J = 5.6 Hz), 8.32 (d, 1H, J = 8.5 Hz), 7.94 (s, 1H), 7.71 (d, 1H, J = 1.5 Hz), 7.64 (d, 1H, J = 3.6 Hz), 7.58 (m, 3H), 7.32 (d, 1H, J = 4.5 Hz), 7.14 (t, 2H, J = 8.8 Hz), 6.92 (d, 1H, J = 3.3 Hz), 5.54 (s, 2H), 3.12 (s, 6H), 2.73 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 538 (M+H)<sup>+</sup>, 205.

5

### Example 52

Preparation of 1-N, N-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]fur-2-oyl}indole.

Step 1: 5-hydroxymethyl-2-carboethoxyfuran.

10        A solution of 5-acetoxymethyl-2-ethoxycarbonylfuran (Maybridge Chemical Co., Ltd., Tintagel, Cornwall, UK., 0.54 g, 2.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.352 g, 2.6 mmol) in 5:1 THF/H<sub>2</sub>O (30 mL), was stirred for 17 hours at ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub>,  
15        filtered, and concentrated *in vacuo* to give 5-hydroxymethyl-2-carboethoxyfuran (0.32 g) as a yellow liquid which was used without further purification.

Step 2: 5-Methanesulfonyloxymethyl-2-carboethoxyfuran.

20        To a 0 °C solution of 5-hydroxymethyl-2-carboethoxyfuran (2.94 g, 17.3 mmol), prepared as in step 1, in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added 2,6-lutidine (2.50 mL, 21.5 mmol) and methanesulfonyl chloride (1.50 mL, 19.0 mmol). The reaction mixture was stirred for 40 min at 0 °C, then the cold bath was removed and stirring was continued for 2 hours. The reaction mixture was extracted with 1N aqueous HCl and saturated aqueous NaHCO<sub>3</sub>, and the organic phase was dried over MgSO<sub>4</sub>,  
25        filtered, and concentrated *in vacuo* to give 5-methanesulfonyloxymethyl-2-carboethoxyfuran (4.0 g) as a yellow oil which was used without further purification.

Step 3: 5-Azidomethyl-2-carboxyethylfuran.

30        To a suspension of NaN<sub>3</sub> (1.3 g, 20 mmol) in CH<sub>3</sub>CN (50 mL) was added the 5-methanesulfonyloxymethyl-2-carboethoxyfuran (4.0 g, 16 mmol) obtained in step 2, and the suspension was warmed to 60 °C and heated for 68 hours. The reaction mixture was cooled to ambient temperature and extracted with saturated aqueous NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*  
35        to give 5-azidomethyl-2-carboxyethylfuran (3.6 g) as an orange oil.

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Step 4: 5-Aminomethyl-2-carboxyethylfuran.

Treatment of a solution in ethanol (50 mL) at ambient temperature of 5-azidomethyl-2-carboxyethylfuran (585 mg, 3.00 mmol), prepared as in step 3, with Raney nickel 2800 and 4 atmospheres of H<sub>2</sub> for 24 hours, followed by filtration of the  
5 reaction mixture and concentration *in vacuo* gave 5-aminomethyl-2-carboxyethylfuran (0.50 g) as a yellow oil.

Step 5: 5-[N-(3-Nitropyrid-4-yl)aminomethyl]-2-carboxyethylfuran.

The desired compound was prepared by heating a solution in CH<sub>3</sub>CN of 5-aminomethyl-2-carboxyethylfuran with 4-ethoxy-3-nitropyridine.  
10

Step 6: 5-[N-(3-aminopyrid-4-yl)aminomethyl]-2-carboxyethylfuran.

The desired compound was prepared by reduction of 5-[N-(3-nitropyrid-4-yl)aminomethyl]-2-carboxyethylfuran, prepared as in step 5, with tin(II) chloride.  
15

Step 7: 5-[(1H-2-Methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-ethoxycarbonylfuran.

The desired compound was prepared by reaction of 5-[N-(3-aminopyrid-4-yl)aminomethyl]-2-carboxyethylfuran, prepared as in step 6, with acetic anhydride and acetic acid as described in Example 3, step 1.  
20

Step 8: 1-N, N-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]fur-2-oyl}indole.

The desired compound was prepared according to the method of Example 51, steps 4-6, except substituting 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-ethoxycarbonylfuran, prepared as in step 7, for 5-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]-2-carboxymethylthiophene. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 9.03 (s, 1H), 8.44 (d, 1H J = 6 Hz), 8.32 (d, 1H, J = 8 Hz), 8.04 (s, 1H), 7.71 (d, 1H, J = 2 Hz), 7.64 (d, 1H, J = 4 Hz), 7.58 (m, 2H), 7.32 (d, 1H, J = 4.5 Hz), 7.14 (t, 2H, J = 8.8 Hz), 6.82 (d, 1H, J = 3 Hz), 6.52 (d, 1H, J = 3 Hz), 5.45 (s, 2H), 3.07 (s, 30 6H), 2.73 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 522 (M+H)<sup>+</sup>, 171.

**Example 53**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]thiazo-2-oyl}indole.

Step 1: 4-Chloromethyl-2-ethoxycarbonylthiazole.

5           A mixture of ethyl thiooxamate (1.0 g, 7.5 mmol) and 1,3-dichloroacetone (1.0 g, 8.3 mmol) in ethanol (25 mL) was heated at reflux for 15 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give  
10 an orange oil. 4-chloromethyl-2-ethoxycarbonylthiazole was obtained as a yellow oil by chromatography on silica gel (10% ether/hexanes).

Step 2: Potassium 4-chlormethyl-2-thiazocarboxylate.

15           To a solution of 4-chloromethyl-2-ethoxycarbonylthiazole (354 mg, 1.73 mmol), prepared as in step 1, in ethanol (10 mL) was added KOH (116 mg, 2.07 mmol). The reaction mixture was stirred for 1 hour at ambient temperature, then concentrated *in vacuo* and azeotroped twice with THF to give potassium 4-chlormethyl-2-thiazocarboxylate.

20           Step 3: 4-Chloromethyl-2-thiazocarbonyl chloride.

          The desired compound is prepared by treatment of a suspension of potassium 4-chlormethyl-2-thiazocarboxylate in THF/DMF with oxalyl chloride.

25           Step 4: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]thiazo-2-oyl}indole.

          The desired compound is prepared according to the method of Example 4, except substituting 4-chloromethyl-2-thiazocarbonyl chloride, prepared as in step 3, for 4-chloromethylbenzoyl chloride.

30

**Example 54**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]thiazo-2-oyl}indole.

          The desired compound is isolated by chromatography on silica gel from the mixture of products formed in Example 53, step 4.

35



**Example 55**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyloxime}indole.

- The desired compound is prepared by reaction of 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 4, with hydroxylamine hydrochloride and pyridine in ethanol as described in WO 93/01813.

**Example 56**

- 10 Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoylhydrazone}indole.

- The desired compound is prepared by treatment of 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 4, with hydrazine as described in  
15 WO 93/01813.

**Example 57**

Preparation of 1-*N,N*-Dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

- 20 Step 1: 3-(4-methylthiophenyl)indole.

- To a -10 °C solution of indole (5.85 g, 50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added triethylamine (7.0 mL, 50 mmol). In a separate flask a solution of p-tolyldisulfide (6.16 g, 25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was cooled to -20 °C and sulfonyl chloride (2.0 mL, 25 mmol) was added over 10 min. The cold bath was  
25 removed and the reaction mixture was stirred for 1 hour and then was added to the indole/triethylamine solution over 15 min. The resulting solution was warmed to ambient temperature and stirred for 17 hours. The reaction mixture was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was taken up in toluene and filtered through a plug of silica gel. The filtrate was  
30 diluted with an equal volume of hexanes and the resulting solid was collected to give 4.43 g of the desired material. The mother liquors were concentrated *in vacuo* and the residue was purified by chromatography on silica gel (10% ethyl acetate/hexanes). The material from the chromatography was combined with the original solid and recrystallized from toluene/hexanes to give 7.41 g (62% yield) of 3-(4-methylthiophenyl)indole. mp 125-126.4 °C.  
35

Step 2: 1-Phenylsulfonyl-3-(4-methylthiophenyl)indole.

To a solution of 3-(4-methylthiophenyl)indole (7.34 g, 30.7 mmol), prepared as in step 1, in dimethoxyethane (75 mL) was added powdered KOH (85%, 7.01 g, 125 mmol) and benzenesulfonyl chloride (4.25 mL, 33.3 mmol). A white precipitate  
5 formed immediately and the reaction mixture became quite warm. The reaction mixture was stirred for 1 hour during which time it cooled to ambient temperature. Water (50 mL) was added and the mixture was extracted with ethyl acetate. The organic phase was washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. 1-phenylsulfonyl-3-(4-methylthiophenyl)indole (8.89 g, 76%  
10 yield) was obtained by chromatography on silica gel (10%, then 20% ethyl acetate/hexanes).

Step 3: 1-Phenylsulfonyl-3-(4-methylphenylsulfonyl)indole.

To a solution of 1-phenylsulfonyl-3-(4-methylthiophenyl)indole (8.89 g, 23.4  
15 mmol) in glacial acetic acid (15 mL) was added 30% H<sub>2</sub>O<sub>2</sub> solution (2.45 g, 72 mmol) and the resulting 2-phase mixture was heated at reflux for 30 min during which time it became a solid mass. The reaction mixture was cooled to ambient temperature and diluted with H<sub>2</sub>O and ethyl acetate and the solid was filtered off. The filtrate layers were separated and the organic phase was washed with saturated aqueous  
20 NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was triturated with ethyl acetate/ether and the resulting solid was combined with the solid obtained above and recrystallized from ethyl acetate to give 8.15 g of 1-phenylsulfonyl-3-(4-methylphenylsulfonyl)indole. mp 188.9-189.7 °C.

Step 4: 1-Phenylsulfonyl-3-[(4-bromomethyl)phenylsulfonyl]indole.

To a suspension of 1-phenylsulfonyl-3-(4-methylphenylsulfonyl)indole (7.33 g, 17.8 mmol) and *N*-bromosuccinimide (3.20 g, 17.9 mmol) in CCl<sub>4</sub> (750 mL) was added benzoyl peroxide (100 mg, 0.40 mmol) and the reaction mixture was warmed to reflux, during which time it became homogenous. The reaction mixture was heated  
30 for 3 hours at reflux, cooled to ambient temperature, stirred for 17 hours, and concentrated *in vacuo*. Pure (1.14 g, mp 194-195.5 °C), and 75% pure (3.74 g) 1-phenylsulfonyl-3-[(4-bromomethyl)phenylsulfonyl]indole was obtained by chromatography on silica gel (20%, then 30%, then 50% CH<sub>2</sub>Cl<sub>2</sub>/toluene) followed by recrystallization from toluene/hexanes.

Step 5: 1-Phenylsulfonyl-3-[(4-(di-*tert*-butoxycarbonyl)aminomethyl)phenylsulfonyl]indole.

To a suspension in DMF (10 mL) of potassium bis(*tert*-butoxycarbonyl)amide (1.78 g, 6.99 mmol), prepared as described by Allan, R.D., et al, *J. Chem. Soc. Perkin Trans. I*, **1983**, 2983, was added a solution of 1-phenylsulfonyl-3-[(4-bromomethyl)phenylsulfonyl]indole (2.8 g, 5.7 mmol), prepared as in step 4, in DMF (12 mL). The reaction mixture was heated at 50 °C for 2 hours, then cooled to ambient temperature and diluted with ethyl acetate (20 mL). The suspension was filtered and the filtrate concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with 1N aqueous NaHSO<sub>4</sub>, H<sub>2</sub>O, 5% aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (1:1 toluene/CH<sub>2</sub>Cl<sub>2</sub>, then CH<sub>2</sub>Cl<sub>2</sub>, then 5% ethyl acetate/CH<sub>2</sub>Cl<sub>2</sub>), followed by recrystallization from toluene/hexanes gave 1-phenylsulfonyl-3-[(4-(di-*tert*-butoxycarbonyl)aminomethyl)phenylsulfonyl]indole (3.10 g, 85% yield). mp 175.5-177 °C.

Step 6: 1-Phenylsulfonyl-3-[(4-aminomethyl)phenylsulfonyl]indole.

A mixture of 1-phenylsulfonyl-3-[(4-(di-*tert*-butoxycarbonyl)aminomethyl)phenylsulfonyl]indole (3.00 g, 4.79 mmol), prepared as in step 5, CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and trifluoroacetic acid (5 mL) was stirred for 45 min at ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (150 mL) and 1M aqueous Na<sub>2</sub>CO<sub>3</sub>. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with H<sub>2</sub>O and brine, and concentrated *in vacuo* to give 1-phenylsulfonyl-3-[(4-aminomethyl)phenylsulfonyl]indole (2.10 g) which was used without further purification.

Step 7: 3-[(4-(*N*-3-Nitropyrid-4-yl)aminomethyl)phenylsulfonyl]indole.

A solution of 1-phenylsulfonyl-3-[(4-aminomethyl)phenylsulfonyl]indole (2.10 g, 4.79 mmol), prepared in step 6, and 4-ethoxy-3-nitropyridine (0.894 g, 5.31 mmol) in ethanol (20 mL) and triethylamine (1 mL) was heated at reflux for 70 hours. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (250 mL). The organic phase was washed twice with H<sub>2</sub>O and once with brine. The combined aqueous washings were extracted with ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (ethyl acetate, then 0.2% ethanol/ethyl acetate) followed by

recrystallization from ethyl acetate/ether gave 3-[(4-(*N*-3-nitropyrid-4-yl)aminomethyl)phenylsulfonyl]indole (350 mg, 23% yield). mp 97-102 °C.

Step 8: 3-{4-[(1*H*-2-Methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

- 5        A mixture of iron powder (140 mg), 3-[(4-(*N*-3-nitropyrid-4-yl)aminomethyl)phenylsulfonyl]indole (483 mg, 0.88 mmol), 1M aqueous NH<sub>4</sub>Cl (5 mL), and CH<sub>3</sub>CN (10 mL) was heated at reflux for 2 hours. The reaction mixture was filtered hot and the filter cake was rinsed with hot methanol. The filtrate was concentrated to a volume of ~2 mL. The liquid was decanted and the residue dried to  
10        give crude 3-[(4-(*N*-3-aminopyrid-4-yl)aminomethyl)phenylsulfonyl]indole (670 mg). To this material was added acetic acid (3 mL) and acetic anhydride (3 mL) and the mixture was heated at reflux for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between 4*N* aqueous NH<sub>4</sub>OH and ethyl acetate/CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with H<sub>2</sub>O and brine, dried over  
15        Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (7%, then 10% methanol/CH<sub>2</sub>Cl<sub>2</sub>) followed by recrystallization from methanol/H<sub>2</sub>O gave 3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole (327 mg). mp 291-293 °C.

- 20        Step 9: 1-*N,N*-Dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

- The desired compound was prepared according to the method of Example 2, except substituting 3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole, prepared as in step 8, for 6-(4-fluorophenyl)-3-{4-  
25        [(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}indole, and substituting 1,2-dimethoxyethane for THF/DMF. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.54 (s, 3H), 3.09 (s, 6H), 5.36 (s, 2H), 7.10 (dd, 1H, *J*=6.0, 0.9 Hz), 7.12 (d, 2H, *J*=8.4 Hz), 7.29 (td, 1H, *J*=7.5, 1.5 Hz), 7.58 (dt, 1H, *J*=8.4, 2.4 Hz), 7.87 (dt, 1H, *J*=7.5, 2.4 Hz), 7.95 (t, 1H, *J*=1.8 Hz), 7.96 (s, 1H), 7.99 (t, 1H, *J*=1.8 Hz), 8.33 (d, 1H, *J*=6.0), 9.01 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 474 (M+H)<sup>+</sup>. Anal Calcd for C<sub>25</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>S · 0.5H<sub>2</sub>O: C, 52.65; H, 5.26, N, 13.53. Found C, 62.29; H, 5.31; N, 13.71. S: calcd 6.19, found 6.22.
- 30

**Example 58**

Preparation of 1-Methyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylsulfonylamino}indole.

Step 1: 1-Methyl-3-[4-(azidomethyl)phenylsulfonylamino]indole.

5 A mixture of 4-azidomethylphenylsulfonyl azide (2.93 g, 12.3 mmol), prepared by reaction of *p*-toluenesulfonyl chloride with *N*-bromosuccinimide followed by sodium azide, and 1-methylindole was heated at 55 °C for 6 hours. Pure 1-methyl-3-[4-(azidomethyl)phenylsulfonylamino]indole was obtained by chromatography on silica gel (1:1 CH<sub>2</sub>Cl<sub>2</sub>/hexanes, then CH<sub>2</sub>Cl<sub>2</sub>, then 1.5% methanol/CH<sub>2</sub>Cl<sub>2</sub>).

10

Step 1: 1-Methyl-3-[4-(aminomethyl)phenylsulfonylamino]indole.

To a solution of 1-methyl-3-[4-(azidomethyl)phenylsulfonylamino]indole (674 mg, 1.97 mmol), prepared as in step 1, in 8:2 THF/H<sub>2</sub>O (10 mL) was added triphenylphosphine (1.03 g, 3.9 mmol) and the reaction mixture was stirred for 17  
15 hours at ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-methyl-3-[4-(aminomethyl)phenylsulfonylamino]indole (1.68 g) as a yellow-orange foam.

20 Step 3: 1-Methyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylsulfonylamino}indole.

The desired compound is prepared according to the method of Example 52, steps 5-8, except substituting 1-methyl-3-[4-(aminomethyl)phenylsulfonylamino]indole, prepared as in step 2, for 5-aminomethyl-  
25 2-carboxyethylfuran.

**Example 59**

Preparation of 1-*p*-Toluenesulfonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole.

30 The desired compound was prepared according to the method of Example 4, except substituting *p*-toluenesulfonyl chloride for *N,N*-dimethylcarbamoyl chloride. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.32 (s, 3H), 2.61 (s, 3H), 5.69 (s, 2H), 7.30-7.45 (m, 6H), 7.64 (dd, 1H, *J* = 5.4, 1.2 Hz), 7.70 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.7-7.8 (m, 2H), 7.91 (apparent d, 2H, *J* = 8.4 Hz), 8.05-8.10 (m, 3H), 8.21 (d, 1H, *J* = 9.0 Hz), 8.27 (s, 1H), 8.33 (d, 1H, *J* = 5.4 Hz), 8.88 (d, 1H, *J* = 1.2 Hz). MS  
35

75

(DCI/NH<sub>3</sub>) m/e 615 (M+H)<sup>+</sup>. Anal calcd for C<sub>36</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>3</sub>S · 1.4H<sub>2</sub>O: C, 67.57; H, 4.69; N, 8.76. Found: C, 67.55; H, 4.51; N, 8.72.

### Example 60

5 Preparation of 1-(Morpholin-4-ylcarbonyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole, and substituting 4-morpholinecarbonyl  
10 chloride for *N,N*-dimethylcarbamoyl chloride. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 3.5-3.6 (m, 4H), 3.6-3.7 (m, 4H), 5.67 (s, 2H), 7.3-7.4 (m, 4H), 7.6-7.7 (m, 2H), 7.7-7.8 (m, 2H), 7.87 (apparent d, 2H, J = 8.1 Hz), 7.85-7.90(narrow m, 1H), 8.12 (s, 1H), 8.30 (d, 1H, J = 8.4 Hz), 8.32 (d, 1H, J = 5.4  
15 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 574 (M+H)<sup>+</sup>.

### Example 61

Preparation of 1-(*N,N*-Dimethylcarbamoylmethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole.

20 The desired compound was prepared according to the method of Example 2, except substituting 6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole for 6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole, and substituting *N,N*-dimethylchloroacetamide for *N,N*-dimethylcarbamoyl chloride. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>,  
25 300 MHz) δ 2.60 (s, 3H), 2.84 (s, 3H), 3.09 (s, 3H), 5.76 (s, 2H), 7.25-7.35 (m, 4H), 7.56 (dd, 1H, J = 8.4, 1.8 Hz), 7.76 (apparent d, 2H, J = 8.4 Hz), 7.7-7.8 (m, 3H), 7.92 (s, 1H), 8.30 (d, 1H, J = 8.1 Hz), 8.31 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 546 (M+H)<sup>+</sup>.

30

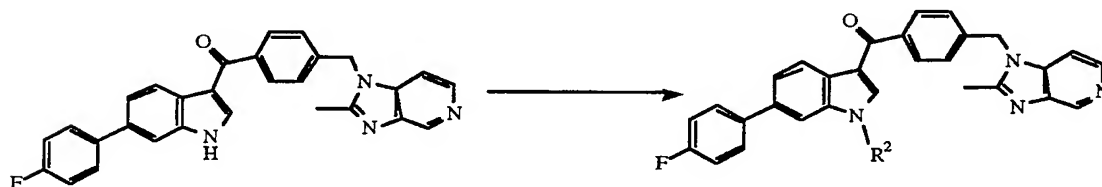
35

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The compounds represented in Table 3 are prepared from 6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyridyl)methyl]benzoyl}indole by the methods described in Examples 59-61 and WO 93/01813.

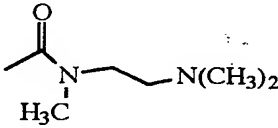
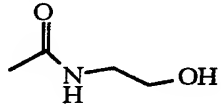
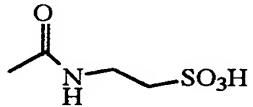
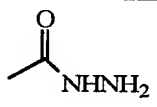
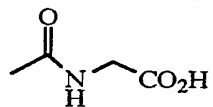



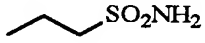
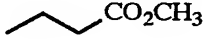
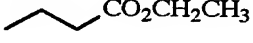
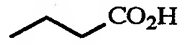
5

Table 3



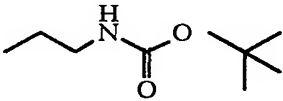

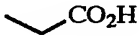
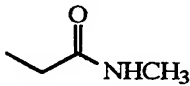
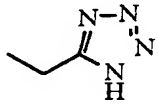
Example	R <sup>2</sup>
62	-CH <sub>3</sub>
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81	
82	
83	
84	
85	
86	-SO <sub>2</sub> CH <sub>3</sub>
87	-SO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
88	-SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
89	-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>

**Example 90**

Preparation of 4,7-Dimethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

5 Step 1: 4,7-Dimethoxycarbonylindole.

To a solution under N<sub>2</sub> of dimethyl nitroterephthalate (10.0 g, 41.8 mmol) in dry, freshly distilled THF (420 mL) at -45 to -40 °C was added vinylmagnesium bromide (1.0 M in THF, 125 mL, 125 mmol) over 10 minutes and the reaction mixture was stirred for an additional 40 minutes. The reaction was quenched with

10 saturated aqueous NH<sub>4</sub>Cl and extracted twice with ether. The combined ether extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 11.9 g of orange oil and yellow granular solid. Chromatography on silica gel (3:1 hexane/ethyl acetate) gave 4,7-dimethoxycarbonylindole (1.90 g) as a bright-yellow waxy solid.

Trituration of the mixed fractions with hexane-ethyl acetate gave an additional 0.66 g of product.

Step 2: 4,7-Dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole.

5 To a solution under N<sub>2</sub> of 4,7-dimethoxycarbonylindole (1.87 g, 8.02 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (135 mL) was added ethylmagnesium bromide (3.0 M in ether, 2.70 mL, 8.10 mmol) over 5 minutes. The resulting red-orange suspension was stirred for 10 minutes at ambient temperature and ZnCl<sub>2</sub> (1.0M in ether, 24.1 mL, 24.1 mmol) was added quickly via syringe. After stirring for 20 minutes, during which time the  
10 reaction mixture turned to a light-green suspension, a solution of 4-chloromethylbenzoyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was added over 5 minutes. The reaction mixture was stirred for 3 days at ambient temperature and then was poured into saturated aqueous NH<sub>4</sub>Cl. The layers were separated and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine,  
15 dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a clear-orange oil (3.57 g). Chromatography on silica gel (99:1, then 97:3 CH<sub>2</sub>Cl<sub>2</sub>/acetone) gave a clear-yellow oil which partially crystallized on standing. Azeotroping with CH<sub>2</sub>Cl<sub>2</sub> gave 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole as a yellow solid (0.85 g, 28%).

20

Step 3: 4,7-Dimethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a 0 °C solution under N<sub>2</sub> of 1H-2-methylimidazo[4,5-c]pyridine, (0.32 g, 2.4 mmol) prepared as in Example 3, step 1, in THF (8.0 mL) and DMPU (1,3-  
25 dimethyl-3,4,5,6-tetrahydro-1H-pyridin-2-one, 2.75 mL) was added NaH (95%, 0.23 g, 2.2 mmol), and the mixture was stirred for 30 minutes. In a separate reaction vessel, NaBr (0.23 g, 2.2 mmol) was added to a solution of 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole (0.83 g, 2.2 mmol) in THF (8.5 mL) and DMPU (1.75 mL). The sodium anion solution was then added to the indole/NaBr solution  
30 via cannula over 5 minutes, and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was partitioned between ethyl acetate and saturated aqueous NH<sub>4</sub>Cl. The organic phase was washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a viscous, clear-orange oil (1.1 g). Chromatography on silica gel (40:1, then 20:1, then 12:1 CHCl<sub>3</sub>/methanol) gave a  
35 bright-yellow oil. Azeotroping with CH<sub>2</sub>Cl<sub>2</sub> gave 4,7-dimethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole (40 mg) as a bright-yellow

solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.63 (s, 3H), 3.72 (s, 3H), 4.02 (s, 3H), 5.41 (s, 2H), 7.14 (d, 2H,  $J = 8.5$  Hz), 7.20 (d, 1H,  $J = 5.5$  Hz), 7.62 (d, 1H,  $J = 7.7$  Hz), 7.70 (d, 1H,  $J = 2.9$  Hz), 7.86 (d, 2H,  $J = 8.5$  Hz), 8.01 (d, 1H,  $J = 8.1$  Hz), 8.40 (d, 1H,  $J = 4.8$  Hz), 9.05 (s, 1H), 10.58 (s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  483 (M+H) $^+$ . IR (microscope) 1163 (s), 1198 (m), 1280 (s), 1433 (m), 1520 (m), 1610 (m), 1637 (m), 1721 (s), 2952 (w), 3362 (br)  $\text{cm}^{-1}$ . Anal calcd for  $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_5 \cdot 0.35 \text{H}_2\text{O} \cdot 0.65 \text{CH}_2\text{Cl}_2$ : C, 61.05; H, 4.45; N, 10.30. Found: C, 61.29; H, 4.53; N, 9.91.

10

**Example 91****Preparation of 4,7-Dimethyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.**

The desired compound was prepared according to the method of Example 90, except substituting 4,7-dimethylindole, prepared as described by Dalton, *et al.*, *Aust. J. Chem.*, **1968**, 21, 2053, for 4,7-dimethoxycarbonylindole. mp 146-151  $^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  2.45 (s, 3H), 2.52 (s, 3H), 2.59 (s, 3H), 5.63 (s, 2H), 6.85 (d, 1H,  $J = 7.3$  Hz), 6.94 (d, 1H,  $J = 7.1$  Hz), 7.27 (d, 2H,  $J = 8.3$  Hz), 7.59 (d, 1H,  $J = 5.4$  Hz), 7.60 (s, 1H), 7.80 (d, 2H,  $J = 8.3$  Hz), 8.30 (d, 1H,  $J = 5.6$  Hz), 8.86 (s, 1H), 11.85 (s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  395 (M+H) $^+$ . IR (microscope) 885 (m), 1222 (m), 1299 (m), 1350 (m), 1391 (m)  $\text{cm}^{-1}$ . Anal calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_4\text{O} \cdot 1.2 \text{H}_2\text{O}$ : C, 72.17; H, 5.91; N, 13.46. Found: C, 72.06; H, 5.64; N, 13.55.

**Example 92****Preparation of 4,7-Dimethyl-3-{4-[(3H-2-methylimidazo[4,5-c]pyrid-3-yl)methyl]benzoyl}indole.**

The desired compound was separated by chromatography (30:1, then 20:1, then 14:1, then 11:1, then 10:1  $\text{CHCl}_3$ , methanol) from the 1H isomer prepared in Example 91. mp 219-225  $^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  2.46 (s, 3H), 2.53 (s, 3H), 2.62 (s, 3H), 5.70 (s, 2H), 6.85 (d, 1H,  $J = 7.3$  Hz), 6.94 (d, 1H,  $J = 7.3$  Hz), 7.32 (d, 2H,  $J = 8.3$  Hz), 7.58 (dd, 1H,  $J = 0.8, 5.5$  Hz), 7.61 (s, 1H), 7.81 (d, 2H,  $J = 8.3$  Hz), 8.30 (d, 1H,  $J = 5.4$  Hz), 8.86 (d, 1H,  $J = 0.7$  Hz), 11.85 (s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  395 (M+H) $^+$ , 412 (M+ $\text{NH}_4$ ) $^+$ . IR  $\text{cm}^{-1}$  (microscope) 881 (m), 1162 (m), 1215 (m), 1346 (s), 1381 (m). Anal calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_4\text{O} \cdot 0.8 \text{H}_2\text{O}$ : C, 73.44; H, 5.82; N, 13.70. Found: C, 73.18; H, 5.50; N, 13.45.

**Example 93****Preparation of 7-Benzyloxy-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.**

5        The desired compound was prepared according to the method of Example 90, except substituting 7-benzyloxyindole for 4,7-dimethoxycarbonylindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 5.30 (s, 2H), 5.63 (s, 2H), 6.93 (d, 1H, J = 7.7 Hz), 7.13 (t, 1H, J = 7.9 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.32-7.46 (c, 3H), 7.54-7.60 (c, 2H), 7.62 (d, 1H, J = 5.1 Hz), 7.71 (d, 1H, J = 2.2 Hz), 7.76 (d, 2H, J = 8.5 Hz), 7.80 (d, 1H, J = 8.1 Hz), 8.30 (d, 1H, J = 5.2 Hz), 8.87 (s, 1H), 12.24 (d, 1H, J = 2.6 Hz). MS (DCI/NH<sub>3</sub>) m/e 473 (M+H)<sup>+</sup>. IR, cm<sup>-1</sup> (microscope) 738 (m), 1219 (m), 1248 (m), 1278 (m), 1436 (s). Anal calcd for C<sub>30</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub> · 1.2 H<sub>2</sub>O: C, 72.92; H, 5.38; N, 11.34. Found: C, 72.97; H, 5.30; N, 11.05.

**Example 94****Preparation of 7-(4-Fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.**

20        The desired compound was prepared according to the method of Example 90, except substituting 7-(4-fluorophenyl)indole, prepared as described by Carrera, G.M., and Sheppard, G.S., *Synlett*, **1994**, 93, for 4,7-dimethoxycarbonylindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 5.64 (s, 2H), 7.26 (dd, 1H, J = 1.3, 7.2 Hz), 7.30 (d, 2H, J = 8.1 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.37 (t, 2H, J(F-Hortho, Hortho-Hmeta) = 9.0 Hz), 7.61 (dd, 1H, J = 1.1, 5.5 Hz), 7.64 (dd, 2H, J(F-Hmeta, Hortho-Hmeta) = 5.5, 8.8 Hz), 7.76 (d, 1H, J = 3 Hz), 7.78 (d, 2H, J = 8.5 Hz), 8.26 (dd, 1H, J = 1.1, 7.7 Hz), 8.30 (d, 1H, J = 5.5 Hz), 8.86 (s, 1H), 11.90 (d, 1H, J = 2.6 Hz). MS (DCI/NH<sub>3</sub>) m/e 461 (M+H)<sup>+</sup>. IR, cm<sup>-1</sup> (microscope) 800 (m), 1174 (m), 1225 (s), 1374 (m), 1395 (m). Anal calcd for C<sub>29</sub>H<sub>24</sub>N<sub>4</sub>OF · 0.75 H<sub>2</sub>O: C, 73.48; H, 4.78; N, 11.82. Found: C, 73.60; H, 4.38; N, 11.79.

**Example 95****Preparation of 6-(4-Fluorophenyl)-3-{N-[3-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)propyl]sarcosyl}indole-1-carboxylic acid dimethyl amide.****Step 1: N-tert-butoxycarbonyl-3-bromopropylamine.**

35        To a 0 °C solution of 3-bromopropylamine hydrobromide (10.0 g, 45.7 mmol) in 1:1 aqueous dioxane was added triethylamine (12.8 mL, 91.8 mmol), di-tert-

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butyldicarbonate (20.2 g, 92.6 mmol), and saturated aqueous NaHCO<sub>3</sub> (3 mL). The cold bath was removed and the reaction mixture was stirred for 3.5 hours. The reaction mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with 10% aqueous citric acid and brine, dried over Na<sub>2</sub>SO<sub>4</sub>,  
5 filtered, and concentrated *in vacuo*. Chromatography on silica gel (10:1, then 6:1, then 3:1 hexane, ethyl acetate) gave *N-tert*-butoxycarbonyl-3-bromopropylamine (21.1 g, 79%) as a clear yellow oil.

10 Step 2: 1-(3-*N-tert*-Butoxycarbonylaminoprop-1-yl)-1H-2-methylimidazo[4,5-c]pyridine.

To a solution under N<sub>2</sub> of 1H-2-methylimidazo[4,5-c]pyridine, (2.00 g, 15.0 mmol) prepared as in Example 3, step 1, in THF (35 mL) and DMF (2.0 mL) was added NaH (95%, 0.42 g, 16.6 mmol) over 15 minutes and the reaction mixture was stirred for 80 minutes. The resulting suspension was cooled in an ice-water bath and  
15 a solution of *N-tert*-butoxy-3-bromopropylamine (3.93 g, 16.5 mmol), prepared as in step 1, in THF (5.0 mL) was added via cannula. The cold bath was removed, DMF (20 mL) was added to make a homogenous solution, and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and poured into water. The layers were separated and the organic phase was  
20 washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 5.5 g of a dark oil. Chromatography on silica gel (20:1, then 10:1 CHCl<sub>3</sub>, methanol) gave 1-(3-*N-tert*-butoxycarbonylaminoprop-1-yl)-1H-2-methylimidazo[4,5-c]pyridine (0.58 g) which was contaminated with 8-10% of the  
25 3H isomer.

Step 3: 1-(3-Aminoprop-1-yl)-1H-2-methylimidazo[4,5-c]pyridine.

To a 0 °C solution of 1-(3-*N-tert*-butoxycarbonylaminoprop-1-yl)-1H-2-methylimidazo[4,5-c]pyridine (0.33 g, 1.1 mmol), prepared as in step 2, in CH<sub>2</sub>Cl<sub>2</sub>  
30 (8.8 mL) was added dropwise trifluoroacetic acid (2.20 mL, 28.6 mmol). The cold bath was removed and the reaction mixture was stirred for 20 minutes. The reaction mixture was carefully added to saturated aqueous NaHCO<sub>3</sub> (20 mL). The acidic aqueous phase (pH = 2) was taken to pH = 12-13 with 15% aqueous NaOH. The layers were combined and added to a liquid-liquid continuous extractor and extracted  
35 into CH<sub>2</sub>Cl<sub>2</sub> for 18 hours. Concentration *in vacuo* gave 1-(3-aminoprop-1-yl)-1H-2-methylimidazo[4,5-c]pyridine (0.27 g).

Step 4: 1-(3-*N*-Formylaminoprop-1-yl)-1H-2-methylimidazopyridine.

The desired compound was prepared by reaction of the 1-(3-aminoprop-1-yl)-1H-2-methylimidazo[4,5-*c*]pyridine (0.27 g, 1.1 mmol) prepared in step 3 with ethyl formate according to the method of DeCosta *et al.*, *J. Med. Chem.*, **1994**, 37, 314. Distillation was replaced by chromatography on silica gel (10:1 CHCl<sub>3</sub>, methanol + 1% of 29% aqueous NH<sub>4</sub>OH, then 7:1 CHCl<sub>3</sub>, methanol + 1% of 29% aqueous NH<sub>4</sub>OH) gave 1-(3-*N*-formylaminoprop-1-yl)-1H-2-methylimidazopyridine (0.23 g, 96% yield from step 3).

Step 5: 1-(3-*N*-Methylaminoprop-1-yl)-1H-2-methylimidazopyridine.

The desired compound (0.21 g) was prepared by reduction of 1-(3-*N*-formylaminoprop-1-yl)-1H-2-methylimidazopyridine (0.21 g, 0.96 mmol), prepared as in step 4, with LAH according to the method of DeCosta *et al.*, *J. Med. Chem.*, **1992**, 35, 38, except substituting DME for THF to give 1-(3-*N*-methylaminoprop-1-yl)-1H-2-methylimidazopyridine as a bright yellow oil which was used without further purification.

Step 6: 6-(4-Fluorophenyl)-3-{N-[3-(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)propyl]sarcosyl}indole.

To a solution under N<sub>2</sub> of the 1-(3-*N*-methylaminoprop-1-yl)-1H-2-methylimidazopyridine (0.21 g) prepared in step 5 and *N,N*-diisopropylethylamine (0.52 mL, 3.0 mmol) in DMF (1 mL) was added a solution in 1:1 DMF, THF (6 mL) of 3-chloroacetyl-6-(4-fluorophenyl)indole (0.18 g, 0.62 mmol), prepared as in Example 23, step 1, and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and extracted twice with aqueous 1N NaOH. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a clear orange foam. Chromatography on silica gel (50:1 CHCl<sub>3</sub>, methanol + 0.5% NH<sub>4</sub>OH, then 20:1 CHCl<sub>3</sub>, methanol + 0.5% NH<sub>4</sub>OH, then 10:1 CHCl<sub>3</sub>, methanol + 0.5% NH<sub>4</sub>OH) to give 6-(4-fluorophenyl)-3-{N-[3-(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)propyl]sarcosyl}indole (21 mg) as an orange, oily foam.

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Step 7: 6-(4-Fluorophenyl)-3-{N-[3-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)propyl]sarcosyl}indole-1-carboxylic acid dimethyl amide.

The desired compound was prepared as an 85:15 mixture of the 1H and 3H isomers by reaction of 6-(4-fluorophenyl)-3-{3-[*N*-methyl-*N*-methylcarbonyl-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)amino]prop-1-yl}indole, prepared as in step 6, with KOH and *N,N*-dimethylcarbamoyl chloride in THF/DMF as described in Example 2.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.96 (quintet, 2H, J = 7.0 Hz), 2.32 (s, 3H), 2.47-2.56 (c, 2H), 2.59 (s, 3H), 3.05 (s, 6H), 3.76 (s, 2H), 4.25 (t, 2H, J = 7.2 Hz), 7.30 (t, 2H, J(F-Hortho, Hortho-Hmeta) = 8.8 Hz), 7.57 (dd, 1H, J = 0.7, 5.5 Hz), 7.60 (dd, 1H, J = 1.5, 8.5 Hz), 7.74 (dd, 2H, J(F-Hmeta, Hortho-Hmeta) = 5.5, 8.8 Hz), 7.79 (d, 1H, J = 1.1 Hz), 8.24 (d, 1H, J = 5.5 Hz), 8.30 (d, 1H, J = 8.1 Hz), 8.66 (s, 1H), 8.78 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 527 (M+H)<sup>+</sup>. IR, cm<sup>-1</sup> (microscope) 822 (m), 1160 (m), 1177 (m), 1391 (s), 1480 (m). Anal calcd for C<sub>30</sub>H<sub>31</sub>N<sub>6</sub>O<sub>2</sub>F · 0.6 H<sub>2</sub>O · 0.2 Et<sub>2</sub>O: C, 66.99; H, 6.24; N, 15.22. Found: C, 67.22; H, 6.00; N, 14.87.

### Example 96

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 4-methoxycarbonyl-3-(3-fluoro-4-methylbenzoyl)indole.

The desired compound was prepared according to the method of Example 90, step 2, except substituting 4-methoxycarbonylindole for 4,7-dimethoxycarbonylindole, and substituting 3-fluoro-4-methylbenzoyl chloride, prepared by reaction of 3-fluoro-4-methylbenzoic acid with thionyl chloride, for 4-chloromethylbenzoyl chloride.

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(3-fluoro-4-methylbenzoyl)indole.

The desired compound was prepared by reaction of 4-methoxycarbonyl-3-(3-fluoro-4-methylbenzoyl)indole, prepared as in step 1, with KOH and *N,N*-dimethylcarbamoyl chloride in THF as described in Example 2.

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Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(3-fluoro-4-bromomethylbenzoyl)indole.

The desired compound was prepared by heating a solution in CCl<sub>4</sub> of *N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(3-fluoro-4-methylbenzoyl)indole, prepared as in step 2, *N*-bromosuccinimide, and catalytic AIBN.

Step 4: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 90, step 3, except substituting *N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(3-fluoro-4-bromomethylbenzoyl)indole, prepared as in step 3, for 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.86 (s, 1H), 8.31-8.29 (d, 1H, J = 4.4 Hz), 8.19 (s, 1H), 7.88-7.85 (d, 1H, J = 8.5 Hz), 7.71-7.69 (d, 1H, J = 4.4 Hz), 7.66-7.63 (d, 1H, J = 4.4 Hz), 7.59-7.56 (d, 1H, J = 4.4 Hz), 7.49-7.46 (d, 1H, J = 8.1 Hz), 7.16-7.10 (t, 1H, J = 7.8 Hz), 5.69 (s, 2H), 3.51 (s, 3H), 3.34 (s, 6H), 2.62 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 514 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>4</sub> · 0.5 CH<sub>2</sub>Cl<sub>2</sub>: C, 61.56; H, 4.53; N, 12.13. Found: C, 61.55; H, 4.51; N, 12.28.

**Example 97**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-benzyloxy-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 90, except substituting 6-benzyloxyindole for 4-methoxycarbonylindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.86 (s, 1H), 8.31-8.29 (d, 1H, J = 5.1 Hz), 8.13-8.10 (d, 1H, J = 8.8 Hz), 7.95 (s, 1H), 7.83-7.80 (d, 2H, J = 5.0 Hz), 7.50-7.47 (d, 2H, J = 5.0 Hz), 7.43-7.37 (t, 1H, J = 6.9 Hz), 7.35-7.33 (d, 2H, J = 5.5 Hz), 7.30-7.26 (d, 2H, J = 7.8 Hz), 7.18 (s, 1H), 7.09-7.06 (d, 1H, J = 5.5 Hz), 5.56 (s, 2H), 5.17 (s, 2H), 2.95 (s, 6H), 2.59 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 544 (M+H)<sup>+</sup>. Anal calcd for C<sub>33</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub> · 1.5 H<sub>2</sub>O: C, 69.45; H, 5.65; N, 12.27. Found: C, 69.45; H, 5.57; N, 11.64.



**Example 98**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]thien-2-oyl}indole.

5 Step 1: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(5-bromomethylthien-2-oyl)indole.

The desired compound was prepared according to the method of Example 96, steps 1-3, except substituting 5-methylthiophene-2-carboxylic acid for 3-fluoro-4-methylbenzoic acid.

10 Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(5-azidomethylthien-2-oyl)indole.

To a solution of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(5-bromomethylthien-2-oyl)indole (2.8 g, 6.2 mmol), prepared as in step 1, in CH<sub>3</sub>CN (10 mL) was added sodium azide (0.77 g, 11.8 mmol) and benzyltrimethylammonium chloride (0.10 g, 0.40 mmol). The reaction mixture was stirred for 3.5 hours at  
15 ambient temperature and then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(5-azidomethylthien-2-oyl)indole (2.18 g) as a yellow foam which was used without  
20 further purification.

Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(5-aminomethylthien-2-oyl)indole.

To a solution of SnCl<sub>2</sub> (4.73 g, 25 mmol) in methanol (70 mL) was added in  
25 2-mL portions a solution in methanol (30 mL) of the 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(5-azidomethylthien-2-oyl)indole prepared in step 2. The reaction mixture was stirred at ambient temperature for 5 hours and then was concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in*  
30 *vacuo* to give a yellow foam (1.60 g). Chromatography on silica gel (1% triethylamine, 99% CH<sub>2</sub>Cl<sub>2</sub>, then 1% triethylamine, 3% methanol, 94% CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(5-aminomethylthien-2-oyl)indole (0.95 g) as a tan foam.

Step 4: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[5-(*N*-3-nitropyridin-4-yl)aminomethylthien-2-oyl]indole.

To a solution of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(5-aminomethylthien-2-oyl)indole (0.896 g, 2.33 mmol) in CH<sub>3</sub>CN (5 mL) was added  
5 4-ethoxy-3-nitropyridine (0.428 g, 2.55 mmol) and the reaction mixture was heated at reflux for 17 hours, then the solvent was removed in vacuo and the residue heated at 100 °C for 2 hours. The reaction mixture was then put under high vacuum to give 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[5-(*N*-3-nitropyridin-4-yl)aminomethylthien-2-oyl]indole as a brown foam which was used without further  
10 purification.

Step 5: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[5-(*N*-3-aminopyridin-4-yl)aminomethylthien-2-oyl]indole.

To a solution of SnCl<sub>2</sub> in methanol (30 mL) was added in 2 mL portions a  
15 solution in 2:1 methanol, CH<sub>2</sub>Cl<sub>2</sub> of the 3-[5-(*N*-3-nitropyridin-4-yl)aminomethylthien-2-oyl]indole prepared in step 4 (1.18 g), and the reaction mixture was stirred for 3 hours at ambient temperature. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The resulting emulsion was filtered after which layers formed. The layers were separated and the organic phase  
20 was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[5-(*N*-3-aminopyridin-4-yl)aminomethylthien-2-oyl]indole (1.73 g) which was used without further purification.

Step 6: 1-*N,N*-Dimethylcarbamoyl-methoxycarbonyl-3-{5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]thien-2-oyl}indole.

A mixture of the 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[5-(*N*-3-aminopyridin-4-yl)aminomethylthien-2-oyl]indole prepared in step 5, acetic acid (20 mL), and acetic anhydride (20 mL) were stirred overnight at reflux. The reaction  
30 mixture was cooled to ambient temperature, quenched by dropwise addition of methanol (30 mL), and concentrated *in vacuo*. The residue was partitioned between saturated aqueous NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 0.83 g of red-brown gum. Chromatography on silica gel (99:1 CH<sub>2</sub>Cl<sub>2</sub>, triethylamine, then 97:2:1 CH<sub>2</sub>Cl<sub>2</sub>,  
35 methanol, triethylamine) gave 1-*N,N*-dimethylcarbamoyl-methoxycarbonyl-3-{5-

[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole (0.14 g) as a brown solid.

Step 7: 1-*N,N*-Dimethylcarbamoyl-methoxycarbonyl-3-{5-[(1H-2-

5 methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole hydrochloride.

A solution of 1-*N,N*-dimethylcarbamoyl-methoxycarbonyl-3-{5-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole (0.125 g), prepared in step 6, in THF was swirled with activated carbon and filtered. To the filtrate was added 4 M HCl/dioxane (0.07 mL). 1-*N,N*-dimethylcarbamoyl-methoxycarbonyl-3-{5-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole hydrochloride (71 mg) was isolated as a light brown powder by filtration. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.84 (s, 1H), 8.36 (d, 1H, J = 6 Hz), 8.30 (s, 1H), 7.97 (dd, 1H, J = 1, 9 Hz), 7.73 (dd, 1H, J = 1, 6 Hz), 7.68 (d, 1H, J = 5 Hz), 7.57 (dd, 1H, J = 1, 7 Hz), 7.46 (m, 1H), 7.22 (d, 1H, J = 5 Hz), 5.84 (s, 2H), 3.54 (s, 3H), 3.04 (s, 6H), 2.68 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 502 (M+H)<sup>+</sup>, 371, 151. IR cm<sup>-1</sup> (microscope) 3400 (br), 2970, 2950, 2600, 1700, 1640, 1515, 1485. Anal calcd for C<sub>25</sub>H<sub>23</sub>N<sub>5</sub>O<sub>4</sub>S · HCl · C<sub>4</sub>H<sub>10</sub>O · 1.5 H<sub>2</sub>O: C, 56.37; H, 5.83; N, 10.96. Found: C, 56.22; H, 6.05; N, 11.08.

**Example 99**

20 Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole hydrochloride.

Step 1: 4-(1H-2-Methylimidazo[4,5-c]pyrid-1-ylmethyl)nitrobenzene.

To a suspension in CH<sub>3</sub>CN (700 mL) of 1H-2-methylimidazo[4,5-c]pyridine (5.04 g, 37.9 mmol), prepared as in Example 3, step 1, was added tris[2-(2-methoxyethoxy)ethyl]amine (1.3 mL, 4.1 mmol) and KOH (10.6 g, 190 mmol). The suspension was stirred at ambient temperature for 90 minutes and then 4-nitrobenzyl bromide (8.23 g, 38.1 mmol) was added and stirring was continued for 2 hours. The reaction mixture was partitioned between ethyl acetate and pH 7 buffer. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)nitrobenzene (1.07 g) as a tan solid.

Step 2: 4-(1H-2-Methylimidazo[4,5-c]pyrid-1-ylmethyl)aniline.

A suspension of 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)nitrobenzene (1.04 g, 3.9 mmol), prepared as in step 1, and SnCl<sub>2</sub> (3.25 g, 19.9 mmol) in 8:2 ethyl acetate, methanol (100 mL) was stirred vigorously for two hours at ambient

temperature. The reaction mixture poured into 1N aqueous NaOH and extracted twice with ethyl acetate and once with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 0.91 g of an orange foam. The foam was dissolved in 30 mL of methanol and SnCl<sub>2</sub> (3.7 g) was added.  
5 After stirring for 3 hours, the reaction was worked up as above to give 0.79 g of 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)aniline as an orange oil.

Step 3: 6-(4-Fluorophenyl)indole-2-carboxaldehyde.

The desired compound was prepared by Vilsmeier formylation of 6-(4-fluorophenyl)indole using DMF and oxalyl chloride.  
10

Step 4: 1-N,N-Dimethylcarbamoyl-6-(4-fluorophenyl)indole-2-carboxaldehyde.

The desired compound was prepared by reaction of 6-(4-fluorophenyl)indole-2-carboxaldehyde with KOH and N,N-dimethylcarbamoyl chloride in THF/DMF as described in Example 2.  
15

Step 5: 6-(4-Fluorophenyl)indole-2-carboxylic acid.

To a solution in THF (25 mL) and *tert*-butyl alcohol (70 mL) of 1-N,N-dimethylcarbamoyl-6-(4-fluorophenyl)indole-2-carboxaldehyde, prepared as in step 4,  
20 was added 2-methyl-2-butene (2M in THF, 8 mL, 16 mmol), followed by a solution of NaClO<sub>2</sub> (1.2 g, 13 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (2.4 g, 17 mmol) in H<sub>2</sub>O (20 mL). After stirring overnight at ambient temperature, a solution of NaClO<sub>2</sub> (0.25 g) and NaH<sub>2</sub>PO<sub>4</sub> (0.50 g) in H<sub>2</sub>O (10 mL) was added and the reaction mixture was stirred for 2 hours. The organic solvents were stripped off *in vacuo* and the residue was  
25 extracted with ether. The aqueous phase was taken to pH 3 with concentrated HCl, the water was decanted, and the residue was taken up in ethyl acetate. The ethyl acetate solution was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a dark-brown oil (0.53 g). The oil was dissolved in THF and treated with activated carbon. Filtration and concentration *in vacuo* gave 6-(4-fluorophenyl)indole-2-carboxylic acid (0.426 g, 93%) as a red solid.  
30

Step 6: 1-N,N-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole.

To a solution in THF (6 mL) of 6-(4-fluorophenyl)indole-2-carboxylic acid  
35 (0.103 g, 0.32 mmol), prepared as in step 5, was added diisopropylethylamine (0.10 mL, 0.57 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.095 g, 0.37

mmol), and the reaction mixture was stirred at ambient temperature for 15 minutes. A solution of 4-(1H-2-methylimidazo[4,5-c]pyrid-1-ylmethyl)aniline (0.108 g, 0.45 mmol), prepared as in step 2, in THF (4 mL) was added and the reaction mixture was stirred for 15 hours at ambient temperature. The reaction mixture was partitioned  
5 between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to give a tan solid (0.165 g). Chromatography on silica gel (7% methanol, ethyl acetate) gave a mixture of desired compound and starting aniline. Gradient elution on the HPLC (5% to 90% acetonitrile/H<sub>2</sub>O with 1% trifluoroacetic acid) gave 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole (13 mg).  
10

Step 7: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole hydrochloride.

15 The desired compound was prepared by treating a solution of 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole, prepared as in step 6, in CH<sub>2</sub>Cl<sub>2</sub>/CDCl<sub>3</sub> with 4N HCl/dioxane. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.97 (s, 1H), 8.38 (d, 1H, J = 6 Hz), 8.06 (d, 1H, J = 7 Hz), 7.97 (s, 1H), 7.92 (s, 1H), 7.70 (s, 1H), 7.59 (d, 2H, J = 7 Hz), 7.53 (m, 2H), 7.46 (m, 1H), 7.09 (m, 2H), 6.99 (d, 2H, J = 7 Hz), 5.27 (s, 2H, 3.05 (s, 6H), 2.59 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 547 (M+H)<sup>+</sup>.  
20

**Example 100**

Preparation of 1-*N,N*-Dimethylcarbamoyl-5-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

25 The desired compound was prepared according to the method of Example 4, except substituting 5-(4-fluorophenyl)indole for 6-(4-fluorophenyl)indole, and using KI instead of NaBr in step 3. mp 198-203 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.63 (s, 3H), 3.10 (s, 6H), 5.41 (s, 2H), 7.12 (d, 1H, J = 8.4 Hz), 7.15 (t, 2H, J = 8.4 Hz), 7.20 (d, 1H, J = 6.0 Hz), 7.58 (d, 2H, J = 1.5 Hz), 7.61 (d, 1H, J = 5.1 Hz), 7.64 (d, 1H, J = 5.1 Hz), 7.76 (s, 1H), 7.83 (d, 2H, J = 8.4 Hz), 8.38 (d, 1H, J = 6.0 Hz), 8.57 (t, 1H, J = 1.3 Hz), 9.06 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 532 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>26</sub>N<sub>5</sub>O<sub>2</sub>F · 0.3 C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>: C, 71.46; H, 5.13; N, 12.55. Found: C, 71.58; H, 5.17; N, 12.77.  
30  
35

**Example 101**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

Step 1: 3-(4-Methylthiophenyl)-6-(4-fluorophenyl)indole.

- 5           The desired compound was prepared according to the method of Example 57, step 1, except substituting 6-(4-fluorophenyl)indole for indole.

Step 2: 1-*tert*-Butoxycarbonyl-3-(4-methylthiophenyl)-6-(4-fluorophenyl)indole.

- 10           To a suspension in CH<sub>3</sub>CN (40 mL) of 3-(4-methylthiophenyl)-6-(4-fluorophenyl)indole (6.75 g, 20.2 mmol), prepared as in step 1, was added di-*tert*-butyldicarbonate (4.94 g, 22.6 mmol) and 4-dimethylaminopyridine (250 mg, 2.05 mmol). The reaction mixture was stirred for 15 minutes at ambient temperature during which time significant gas evolution occurred and the reaction mixture became a clear solution. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate. The ethyl acetate solution was washed with H<sub>2</sub>O, 1M aqueous NaHSO<sub>4</sub>, H<sub>2</sub>O, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*.  
15           Chromatography on silica gel (1% then 2% ethyl acetate/hexane), followed by crystallization from ether/hexane gave 1-*tert*-butoxycarbonyl-3-(4-methylthiophenyl)-6-(4-fluorophenyl)indole (8.05 g, 92% yield). mp 123.7-124.4 °C.

20

Step 3: 1-*tert*-Butoxycarbonyl-3-(4-methylphenylsulfonyl)-6-(4-fluorophenyl)indole.

- 25           To a 0 °C solution in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) of 1-*tert*-butoxycarbonyl-3-(4-methylthiophenyl)-6-(4-fluorophenyl)indole (8.03 g, 18.5 mmol), prepared as in step 1, was added 3-chloroperbenzoic acid (80%, 8.2 g, 38 mmol). The cold bath was removed and the reaction mixture was stirred for 1 hour. Aqueous 2N Na<sub>2</sub>CO<sub>3</sub> (50 mL) was added and the layers separated. The organic phase was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (10%, then 20% ethyl acetate/hexane), followed by crystallization from ether/hexane gave 1-*tert*-butoxycarbonyl-3-(4-methylphenylsulfonyl)-6-(4-fluorophenyl)indol  
30           (5.99 g), mp 134.6-135.3 °C.

Step 4: 1-*N,N*-Dimethylcarbamoyl-6-(4-fluorophenyl)3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

- 35           The desired compound was prepared according to the method of Example 56, steps 4-9, except substituting 1-*tert*-butoxycarbonyl-3-(4-methylphenylsulfonyl)-6-(4-fluorophenyl)indol, prepared as in step 3, for 1-phenylsulfonyl-3-[(4-

bromomethyl)phenylsulfonyl]indole. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.54 (s, 3H), 3.13 (s, 6H), 5.37 (s, 2H), 7.11 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.4 Hz), 7.14 (d, 1H, J = 8.4 Hz), 7.47-7.58 (c, 3H), 7.75 (d, 1H, J = 1.5 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.00 (d, 2H, J = 8.4 Hz), 8.35 (d, 1H, J = 3.6 Hz), 9.03 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 568 (M+H)<sup>+</sup>. Anal calcd for C<sub>31</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub>SF · 0.40 ethyl acetate: C, 64.95; H, 4.88; N, 11.62. Found: C, 64.85; H, 4.73; N, 11.72.

### Example 102

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-{4-[(1*H*-2-methylimidazo[4,5-  
c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 4, steps 1 and 2, except substituting 4-bromoindole for 6-(4-fluorophenyl)indole.

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-(4-azidomethylbenzoyl)indole.

To a solution in DMF (40 mL) of 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-chloromethylbenzoyl)indole (12.54 g, 31 mmol), prepared as in Step 1, was added sodium azide (2.15 g, 33 mmol). The reaction mixture was stirred for 3 hours at ambient temperature and then was diluted with H<sub>2</sub>O and extracted twice with ethyl acetate. The combined organic extracts were washed twice with H<sub>2</sub>O, once with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-azidomethylbenzoyl)indole (16.0 g) which was used without further purification.

Step 3: 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-(4-aminomethylbenzoyl)indole.

To a solution of the 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-azidomethylbenzoyl)indole prepared in step 2 (16.0 g) in THF (60 mL) was added triphenylphosphine (8.7 g, 33 mmol) and H<sub>2</sub>O (30 mL) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was evaporated to dryness and the residue was dissolved in THF (100 mL). 4N HCl/dioxane (8 mL) was added followed by ether (100 mL) to form a gummy solid which was left standing overnight. The liquid was decanted and the solid was dissolved in H<sub>2</sub>O. The aqueous solution was extracted with ethyl acetate. The ethyl acetate extract was discarded and the aqueous phase was made basic with aqueous 2N Na<sub>2</sub>CO<sub>3</sub> and extracted three times with ethyl acetate. The combined organic extracts were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-

*N,N*-dimethylcarbamoyl-4-bromo-3-(4-aminomethylbenzoyl)indole (13.65 g) which was used without further purification.

5     Step 4: 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-(4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl)indole.

      A mixture of the 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-aminomethylbenzoyl)indole prepared in step 3 (13.65 g) and 4-ethoxy-3-nitropyridine (5.10 g, 30.3 mmol) in CH<sub>3</sub>CN (50 mL) was heated at reflux for 50 hours during which time 46 mL of solvent distilled out. To the thick residue was added toluene (50 mL) and the mixture was heated at a rate such that 21 mL of solvent distilled off over 2 hours. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (30 mL). The solution was placed directly on a silica gel column and eluted with 50%, then 80% ethyl acetate/toluene to give 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl)indole (6.76 g), mp 173.5-174.5 °C after crystallization from ethyl acetate/ether.

Step 5: 1-*N,N*-Dimethylcarbamoyl-4-bromo-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

      The desired compound (4.72 g), was prepared according to the method of Example 57, step 8, except substituting 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl)indole, prepared as in step 4, for 3-[(4-(*N*-3-nitropyrid-4-yl)aminomethyl)phenylsulfonyl]indole and crystallization from CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate. mp 232.5-234 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.56 (s, 3H), 3.01 (s, 6H), 5.63 (s, 2H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.28 (t, 1H, *J* = 8.4 Hz), 7.47 (dd, 1H, *J* = 8.4, 0.3 Hz), 7.57 (dd, 1H, *J* = 5.7, 0.3 Hz), 7.69 (dd, 1H, *J* = 8.4, 0.3 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.03 (s, 1H), 8.38 (d, 1H, *J* = 5.7 Hz), 8.84 (d, 1H, *J* = 0.3 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 516, 518 (*M*+*H*)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>22</sub>N<sub>5</sub>O<sub>2</sub>Br: C, 60.47; H, 4.29; N, 13.56. Found: C, 60.21; H, 4.29; N, 13.38.

30

**Example 103**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-acetyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

      To a 20-mL pressure bottle were added 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (212 mg, 0.41 mmol), prepared as in Example 102, tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.023 mmol), butyl vinyl ether (208 mg, 2.1 mmol), triethylamine (87 mg, 0.86



mmol), and dioxane (5 mL). The bottle was flushed thoroughly with N<sub>2</sub>, sealed, and heated at 130 °C for 24 hours. The reaction mixture was cooled to ambient temperature and placed directly on a silica gel column eluting with 7% methanol, CH<sub>2</sub>Cl<sub>2</sub> to give 193 mg of the intermediate enol ether. The enol ether was stirred for 5 30 minutes in 90% trifluoroacetic acid. The reaction mixture was diluted with H<sub>2</sub>O and concentrated *in vacuo*. The residue was partitioned between 5% aqueous NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. 1-*N,N*-dimethylcarbamoyl-4-acetyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (131 mg) was 10 obtained by chromatography on silica gel (8% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.40 (s, 3H), 2.58 (s, 3H), 3.03 (s, 6H), 5.64 (s, 2H), 7.27 (d, 2H, J = 8.4 Hz), 7.45 (dd, 1H, J = 7.8, 8.1 Hz), 7.57 (dd, 1H, J = 7.8, 0.6 Hz), 7.59 (d, 1H, J = 6.6 Hz), 7.84 (d, 2H, J = 8.4 Hz), 7.84 (dd, 1H, J = 8.1, 0.6 Hz), 8.09 (s, 1H), 8.30 (d, 1H, J = 6.6 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 480 15 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub> · 1.4 H<sub>2</sub>O: C, 66.63; H, 5.55; N, 13.87. Found: C, 66.75; H, 5.70; N, 13.87.

#### Example 104

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(fur-2-yl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole. 20

To a 20-mL pressure bottle were added tri(*n*-butyl)-(fur-2-yl)stannane (160 mg, 0.45 mmol), 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (153 mg, 0.30 mmol), prepared as in Example 102, tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 25 mmol), and dioxane (5 mL). The bottle was flushed thoroughly with N<sub>2</sub>, sealed, and heated at 115 °C for 2.5 hours. The reaction mixture was cooled to ambient temperature, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (7% methanol, CH<sub>2</sub>Cl<sub>2</sub>). The resulting material was taken up in ethyl acetate, and the solution was warmed, diluted with ether, filtered, and concentrated *in vacuo*. Chromatography on silica gel twice (5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave pure 1-*N,N*- 30 dimethylcarbamoyl-4-(fur-2-yl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (94 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.53 (s, 3H), 3.03 (s, 6H), 5.57 (s, 2H), 6.17 (dd, 1H, J = 3.9, 3.6 Hz), 6.36 (dd, 1H, J = 3.9, 0.9 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.26 (dd, 1H, J = 2.4, 0.9 Hz), 7.34 (dd, 1H, J = 8.4, 2.1 Hz), 7.39 (t, 1H, J = 8.4 Hz), 7.57 (dd, 1H, J = 6.3, 1.2 Hz), 7.66 (dd, 35 1H, J = 8.4, 2.1 Hz), 7.67 (d, 2H, J = 8.7 Hz), 8.01 (s, 1H), 8.31 (d, 1H, J = 6.3

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Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 504 (M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub> · 0.2 ethyl acetate · 0.2 H<sub>2</sub>O: C, 70.49; H, 5.19; N, 13.35. Found: C, 70.30; H, 5.10; N, 13.30.

### Example 105

#### 5 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(benzo[b]fur-2-yl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 104, except substituting tri(*n*-butyl)-(benzo[b]fur-2-yl)stannane for tri(*n*-butyl)-(fur-2-yl)stannane. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.49 (s, 3H), 3.07 (s, 6H), 5.47 (s, 2H), 6.87 (s, 1H), 6.91 (dd, 1H, J = 7.8, 1.2 Hz), 6.98 (d, 2H, J = 8.7 Hz), 7.04 (dd, 1H, J = 6.0, 1.2 Hz), 7.08 (td, 1H, J = 6.0, 1.2 Hz), 7.33 (dt, 1H, J = 9.3, 1.2 Hz), 7.47 (t, 1H, J = 7.8 Hz), 7.50 (dd, 1H, J = 6.0, 1.2 Hz), 7.55 (dd, 1H, J = 6.6, 1.2 Hz), 7.58 (d, 2H, J = 8.7 Hz), 7.78 (dd, 1H, J = 9.3, 1.2 Hz), 8.10 (s, 1H), 8.32 (d, 1H, J = 6.6 Hz), 8.87 (s, 1H). Anal calcd for C<sub>34</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub> · 0.4 ethyl acetate · 0.5 H<sub>2</sub>O: C, 71.52; H, 5.26; N, 11.71. Found: C, 71.43; H, 5.35; N, 11.67.

### Example 106

#### 20 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared by heating a mixture of trimethyl-(trimethylsilylethynyl)stannane (58 mg, 0.232 mmol), 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (100 mg, 0.194 mmol), prepared as in Example 102, tetrakis(triphenylphosphine)palladium(0) (16 mg), and toluene (7 mL) were heated in a pressure bottle at 120 °C for 4 hours as described in Example 103. The reaction mixture was cooled to ambient temperature, filtered, and concentrated *in vacuo*. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>, then 5% methanol/CH<sub>2</sub>Cl<sub>2</sub> gave 1-*N,N*-dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (58 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.00 (s, 9H), 2.60 (s, 3H), 3.05 (s, 6H), 5.68 (s, 2H), 7.33 (d, 2H, J = 9 Hz), 7.37-7.40 (m, 1H), 7.62 (d, 1H, J = 6 Hz), 7.70-7.78 (m, 1H), 7.90 (d, 2H, J = 9 Hz), 8.04 (s, 1H), 8.33 (d, 1H, J = 6 Hz), 8.88 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 534 (M+H)<sup>+</sup>. Anal calcd for C<sub>31</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>Si · 0.75 H<sub>2</sub>O: C, 67.83; H, 5.94; N, 12.41. Found: C, 68.04; H, 5.98; N, 12.79.

**Example 107**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a solution in 40:20 THF/CH<sub>3</sub>CN of 1-*N,N*-dimethylcarbamoyl-4-  
5 (trimethylsilylethynyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-  
yl)methyl]benzoyl}indole (0.39 g, 0.73 mmol), prepared as in Example 106, was  
added CsF (0.56 g, 3.66 mmol) and the reaction mixture was stirred for 16 hours at  
ambient temperature. The reaction mixture was filtered and the filtrate was washed  
with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-  
10 dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-  
yl)methyl]benzoyl}indole (0.29 g). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.55 (s, 3H),  
3.00 (s, 6H), 4.04 (s, 1H), 5.64 (s, 2H), 7.25 (d, 2H, *J* = 9 Hz), 7.30-7.42 (m,  
2H), 7.58 (d, 1H, *J* = 6 Hz), 7.73 (d, 1H, *J* = 9 Hz), 7.85 (d, 2H, *J* = 9 Hz), 8.04  
(s, 1H), 8.29 (d, 1H, *J* = 6 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 462 (M+H)<sup>+</sup>.  
15 Anal calcd for C<sub>28</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub> · 2.0 H<sub>2</sub>O: C, 67.21; H, 5.20; N, 13.53. Found: C,  
67.59; H, 5.46; N, 14.07.

**Example 108**

Preparation of 4-(4-Fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-  
yl)methyl]benzoyl}indole.

To a solution in DMF (6 mL) of 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-  
20 [(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (200 mg, 0.38  
mmol), prepared as in Example 102, was added  
tetrakis(triphenylphosphine)palladium(0) (22 mg) and the solution was stirred for 30  
minutes. A solution of 4-fluorophenylboronic acid (80 mg, 0.57 mmol) in DMF (2  
25 mL) was added, followed by saturated aqueous NaHCO<sub>3</sub> (4 mL). The reaction  
mixture was stirred at 90 °C for 4 hours and 40 °C for 48 hours. Additional  
tetrakis(triphenylphosphine)palladium(0) (22 mg) was added and the reaction mixture  
was stirred at 115 °C for 4 hours. The reaction mixture was cooled to ambient  
temperature, diluted with H<sub>2</sub>O, and extracted three times with ethyl acetate. The  
30 combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*.  
Chromatography on silica gel (5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 4-(4-fluorophenyl)-3-{4-  
[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole as a white solid (111  
mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 3.04 (s, 6H), 5.58 (s, 2H),  
6.85 (t, 2H, *J* = 9 Hz), 7.05-7.13 (m, 5H), 7.43 (t, 1H, *J* = 9 Hz), 7.50 (d, 2H, *J* =  
35 9 Hz), 7.60 (d, 1H, *J* = 6 Hz), 7.68 (d, 1H, *J* = 9 Hz), 8.01 (s, 1H), 8.30 (bs, 1H),

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8.88 (bs, 1H). MS (DCI/NH<sub>3</sub>) m/e 532 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>26</sub>N<sub>5</sub>O<sub>2</sub>F: 0.75 H<sub>2</sub>O: C, 70.51; H, 5.08; N, 12.84. Found: C, 70.23; H, 5.16; N, 12.54.

### Example 109

5 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 4-Chloro-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 90, step 2, except substituting 4-chloroindole for 4,7-dimethoxycarbonylindole.

10

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-chloro-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared by reaction of 4-chloro-3-(4-chloromethylbenzoyl)indole, prepared as in step 1, with KOH and *N,N*-dimethylcarbamoyl chloride in THF/DMF as described in Example 2.

15

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 90, step 3, except substituting 1-*N,N*-dimethylcarbamoyl-4-chloro-3-(4-chloromethylbenzoyl)indole, prepared as in step 2, for 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.56 (s, 3H), 3.01 (s, 6H), 5.65 (s, 2H), 7.28 (d, 2H, J = 8.4 Hz), 7.25-7.40 (m, 2H), 7.59 (dd, 1H, J = 6.0, 1.2 Hz), 7.65 (dd, 1H, J = 7.8, 1.2 Hz), 7.86 (d, 2H, J = 8.1 Hz), 8.05 (s, 1H), 8.29 (d, 1H, J = 5.4 Hz), 8.85 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 472 (M+H)<sup>+</sup>.  
25 Anal calcd for C<sub>26</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub> · 1.3 H<sub>2</sub>O: C, 63.04; H, 5.01; N, 14.14. Found: C, 62.92; H, 4.62; N, 13.97.

### Example 110

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-fluoro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

30 The desired compound was prepared according to the method of Example 109, except substituting 4-fluoroindole for 4-chloroindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 3.00 (s, 6H), 5.66 (s, 2H), 7.08 (dd, 1H, J = 11.1, 6.9 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.37 (dt, 1H, J = 8.1, 5.1 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.62 (dd, 1H, J = 5.7, 1.0 Hz), 7.86 (d, 2H, J = 8.7 Hz), 8.04 (s, 1H), 8.31 (d, 35 1H, J = 5.4 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 456 (M+H)<sup>+</sup>. Anal calcd for

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$C_{26}H_{22}FN_5O_2 \cdot 0.2$  ethyl acetate  $\cdot 0.8 H_2O$ : C, 66.03; H, 5.21; N, 14.37. Found: C, 66.16; H, 5.27; N, 14.08.

### Example 111

Preparation of 1-*N,N*-Dimethylcarbamoyl-2-methyl-3-{4-[(1*H*-2-methylimidazo[4.5-  
5 c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 2-methylindole for 4-chloroindole.  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.35 (s, 3H), 2.57 (s, 3H), 5.64 (s, 2H), 6.99 (dt, 1H,  $J = 8.1, 1.0$  Hz), 7.11 (dt, 1H,  $J = 8.1, 1.0$  Hz), 7.2-7.3 (m, 3H), 7.38 (d, 1H,  $J = 8.1$  Hz), 7.58 (d, 10 2H,  $J = 8.1$  Hz), 7.55-7.65 (m, 1H), 8.31 (d, 1H,  $J = 5.4$  Hz), 8.86 (s, 1H). MS (DCI/ $NH_3$ )  $m/e$  381 ( $M+H$ ) $^+$ . Anal calcd for  $C_{24}H_{20}N_4O \cdot 0.4 H_2O$ : C, 74.36; H, 5.41; N, 14.45. Found: C, 74.25; H, 5.35; N, 14.4.

### Example 112

15 Preparation of 1,4-di-*N,N*-Dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-*N,N*-dimethylcarbamoylindole for 4-chloroindole.  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.58 (s, 3H), 2.76 (s, 3H), 2.82 (s, 3H), 3.01 (s, 6H), 20 5.65 (s, 2H), 7.15 (dd, 1H,  $J = 7.2, 1$  Hz), 7.28 (apparent d, 2H,  $J = 8.4$  Hz), 7.35-7.45 (m, 1H), 7.62 (d, 1H,  $J = 5.4$  Hz), 7.67 (apparent d, 2H,  $J = 8.4$  Hz), 8.04 (s, 1H), 8.30 (d, 1H,  $J = 5.4$  Hz), 8.86 (s, 1H). MS (DCI/ $NH_3$ )  $m/e$  509 ( $M+H$ ) $^+$ . Anal calcd for  $C_{29}H_{28}N_6O_3 \cdot 1.4 H_2O$ : C, 65.52; H, 5.82; N, 15.74. Found: C, 65.59; H, 6.02; N, 14.58.

### 25 Example 113

Preparation of 1-*N,N*-Dimethylcarbamoyl-5-methoxycarbonyl-3-{4-[(1*H*-2-  
methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 5-methoxycarbonylindole for 4-chloroindole.  $^1H$  NMR (DMSO-  
30  $d_6$ , 300 MHz)  $\delta$  2.65 (s, 3H), 3.08 (s, 6H), 3.96 (s, 3H), 5.44 (s, 2H), 7.19 (d, 2H,  $J = 8.1$  Hz), 7.29 (d, 1H,  $J = 5.7$  Hz), 7.57 (d, 1H,  $J = 9.0$  Hz), 7.78 (s, 1H), 7.84 (d, 2H,  $J = 8.1$  Hz), 8.11 (dd, 1H,  $J = 9.0, 1.5$  Hz), 8.42 (d, 1H,  $J = 5.7$  Hz), 9.05 (d, 1H,  $J = 1.5$  Hz), 9.06 (s, 1H). MS (DCI/ $NH_3$ )  $m/e$  513 ( $M+NH_4$ ) $^+$ . Anal  
35 calcd for  $C_{28}H_{25}N_5O_4 \cdot 0.7 EtOAc$ : C, 66.39; H, 5.54; N, 12.57. Found: C, 66.36; H, 5.20; N, 12.47.

**Example 114**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methoxycarbonyl-6-(4-fluorophenyl)indole for 4-chloroindole. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.57 (s, 3H), 3.04 (s, 6H), 3.48 (s, 3H), 5.64 (s, 2H), 7.25-7.35 (m, 4H), 7.59 (d, 1H, *J* = 6.4 Hz), 7.75-7.80 (m, 3H), 7.85 (apparent d, 2H, *J* = 8.1 Hz), 8.04 (d, 1H, *J* = 1.7 Hz), 8.14 (s, 1H), 8.30 (d, 1H, *J* = 5.2 Hz), 8.85 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 590 (M+H)<sup>+</sup>. Anal calcd for C<sub>34</sub>H<sub>28</sub>N<sub>5</sub>O<sub>4</sub>F · 1.4 H<sub>2</sub>O: C, 66.42; H, 5.05; N, 11.39. Found: C, 66.41; H, 4.96; N, 10.91.

**Example 115**

Preparation of 4-Methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a 0 °C solution in methanol (4 mL) of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, (164 mg, 0.33 mmol), prepared as in Example 44, was added aqueous 1*N* NaOH (0.9 mL, 0.9 mmol) and the reaction mixture was stirred for 1 hour. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NH<sub>4</sub>Cl. The aqueous phase was acidified with 1*N* aqueous HCl and extracted 4 times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (140 mg) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.58 (s, 3H), 3.51 (s, 3H), 5.63 (s, 2H), 7.2-7.35 (m, 3H), 7.40 (dd, 1H, *J* = 7.3, 1.1 Hz), 7.60 (dd, 1H, *J* = 5.5, 1.1 Hz), 7.69 (dd, 1H, *J* = 8.1, 1.1 Hz), 7.79 (apparent d, 2H, *J* = 8.1 Hz), 7.89 (s, 1H), 8.30 (d, 1H, *J* = 5.6 Hz), 8.86 (s, 1H), 12.17 (br s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 425 (M+H)<sup>+</sup>.

**Example 116**

Preparation of 4-Methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a 0 °C solution in 1:1 THF/DMF (2 mL) of 4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (111 mg, 0.26 mmol), prepared as in Example 115 was added NaH (9.0 mg, 0.39 mmol). After 5 minutes, 1-pyrrolidine carbonyl chloride (42 mg, 0.31 mmol) was added and the yellow suspension was stirred for 1 hour at 0 °C. The reaction mixture was partitioned

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between ethyl acetate and brine. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed twice with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel gave 4-methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (101 mg) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.7-1.8 (br m, 4H), 2.57 (s, 3H), 3.46 (s, 3H), 3.5-3.6 (br m, 4H), 5.64 (s, 2H), 7.28 (apparent d, 2H, J = 8.4 Hz), 7.4-7.5 (m, 1H), 7.55-7.65 (m, 2H), 7.85 (apparent d, 2H, J = 8.4 Hz), 7.98 (dd, 1H, J = 8.4, 1.2 Hz), 8.19 (s, 1H), 8.30 (d, 1H, J = 5.4 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 522 (M+H)<sup>+</sup>.

### Example 117

#### Preparation of 1-N,N-Dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-benzyloxycarbonylindole for 4-chloroindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.6 (s, 3H), 3.01 (s, 6H), 5.01 (s, 2H), 5.67 (s, 2H), 7.0-7.2 (m, 5H), 7.29 (apparent d, 2H, J = 8.1 Hz), 7.4-7.5 (m, 1H), 7.6-7.7 (m, 2H), 7.86 (apparent d, 2H, J = 8.4 Hz), 8.10 (s, 1H), 8.31 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 572 (M+H)<sup>+</sup>. Anal calcd for C<sub>34</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> · 1.1 H<sub>2</sub>O: C, 69.05; H, 5.32; N, 11.84. Found: C, 69.27; H, 5.29; N, 11.26.

### Example 118

#### Preparation of 1-N,N-Dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid.

The desired compound (46 mg) was prepared by hydrogenolysis (1 atm H<sub>2</sub>, 10% palladium on carbon, 7:3 methanol, CH<sub>2</sub>Cl<sub>2</sub>) of 1-N,N-dimethylcarbamoyl-4-benzyloxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 117. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.55 (s, 3H), 3.02 (s, 6H), 5.62 (s, 2H), 7.25 (d, 2H, J = 8.4 Hz), 7.4-7.5 (m, 1H), 7.55-7.65 (m, 2H), 7.81 (d, 2H, J = 8.4 Hz), 7.8-7.9 (m, 1H), 8.03 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.85 (s, 1H), 12.62 (br s, 1H). MS (DCI/NH<sub>3</sub>) m/e 482 (M+H)<sup>+</sup>.

**Example 119**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(*N*-nonylcarbamoyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a suspension of 1-*N,N*-dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid (100 mg, 0.21 mmol), prepared as in Example 118, was added 1-aminononane (46  $\mu$ L, 0.25 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (48 mg, 0.25 mmol), and the resulting clear solution was stirred for 24 hours at ambient temperature. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and brine. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified directly by reverse-phase HPLC (25-60% CH<sub>3</sub>CN/H<sub>2</sub>O with 0.1% trifluoroacetic acid) to give 1-*N,N*-dimethylcarbamoyl-4-(*N*-nonylcarbamoyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (33 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  0.85 (t, 3H, *J* = 6.3 Hz), 1.1-1.3 (m, 14H), 2.57 (s, 3H), 2.82 (q, 2H, *J* = 6.3 Hz), 3.01 (s, 6H), 5.62 (s, 2H), 7.25 (d, 2H, *J* = 8.1 Hz), 7.29 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.3-7.4 (m, 1H), 7.61 (d, 1H, *J* = 5.4 Hz), 7.71 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.77 (d, 2H, *J* = 8.1 Hz), 7.97 (s, 1H), 8.16 (t, 1H, *J* = 5.4 Hz), 8.30 (d, 1H, *J* = 5.7 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 607 (M+H)<sup>+</sup>.

**Example 120**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(dec-1-yloxy carbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a solution in DMF (4 mL) of 1-*N,N*-dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid (200 mg, 0.42 mmol), prepared as in Example 118, was added NaHCO<sub>3</sub> (70 mg, 0.83 mmol) and decyl bromide (0.43 mL, 2.07 mmol). The resulting white suspension was stirred for 72 hours at ambient temperature and then partitioned between CH<sub>2</sub>Cl<sub>2</sub> and brine. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (10% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-4-(dec-1-yloxy carbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (65 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  0.83 (t, 3H, *J* = 6.6 Hz), 1.0-1.35 (m, 16H), 2.57 (s, 3H), 3.02 (s, 6H), 3.90 (t, 2H, *J* = 6.6 Hz), 5.64 (s, 2H), 7.30 (d, 2H, *J* = 8.1 Hz), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 2H), 7.86 (dd, 1H, *J* = 8.1, 1.2 Hz), 7.88 (d, 2H, *J* = 8.4 Hz), 8.10 (s, 5.7 Hz), 8.29 (d, 1H, *J* = 5.7 Hz), 8.85 (s, 1H).



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MS (DCI/NH<sub>3</sub>) m/e 622 (M+H)<sup>+</sup>. Anal calcd for C<sub>37</sub>H<sub>43</sub>N<sub>5</sub>O<sub>4</sub> · 0.4 H<sub>2</sub>O: C, 70.65; H, 7.11; N, 10.90. Found: C, 70.65; H, 7.02; N, 11.13.

### Example 121

5 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methoxyindole for 4-chloroindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.6 (s, 3H), 3.03 (s, 6H), 3.49 (s, 3H), 5.63 (s, 2H), 6.7 (d, 1H, J = 7.5 Hz), 7.18-7.3 (m, 4H), 7.63 (d, 1H, J = 6 Hz), 7.74 (d, 2H, J = 7.5 Hz), 7.85 (s, 1H), 8.31 (d, 1H, J = 6 Hz), 8.88 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 468 (M<sup>+</sup>). Anal calcd for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub> · 0.75 H<sub>2</sub>O: C, 67.41; H, 5.55; N, 14.55. Found: C, 67.71; H, 5.34; N, 13.64.

### Example 122

15 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methylindole for 4-chloroindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 2.96 (s, 6H), 5.64 (s, 2H), 7.05 (d, 1H, J = 6 Hz), 7.25 (d, 1H, J = 6 Hz), 7.27-7.32 (m, 2H), 7.45 (d, 1H, J = 6 Hz), 7.58 (d, 1H, J = 3 Hz), 7.83 (d, 1H, J = 3 Hz), 7.85 (d, 2H, J = 6 Hz), 8.30 (d, 1H, J = 3 Hz), 8.84 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 452 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub> · 0.5 H<sub>2</sub>O: C, 70.56; H, 5.73; N, 14.73. Found: C, 70.41; H, 5.69; N, 15.20.

### Example 123

25 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)hex-6-ylcarbonyl]indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methoxycarbonylindole for 4-chloroindole, and 7-bromoheptanoyl chloride for 4-bromomethylbenzoyl chloride. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.25-1.45 (m, 4H), 1.6-1.8 (m, 4H), 2.57 (s, 3H), 2.87 (t, 2H, J = 7.4 Hz), 3.05 (s, 3H), 3.73 (s, 3H), 4.20 (t, 2H, J = 7.4 Hz), 7.4-7.45 (narrow m, 2H), 7.56 (dd, 1H, J = 5.4, 0.6 Hz), 7.7-7.8 (complex m, 1H), 8.25 (d, 1H, J = 5.4 Hz), 8.59 (s, 1H), 8.79 (d, 1H, J = 0.6 Hz). MS (DCI/NH<sub>3</sub>) m/e 490 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub> · 0.6 H<sub>2</sub>O: C, 64.81; H, 6.49; N, 14.00. Found: C, 64.91; H, 6.32; N, 13.92.

**Example 124**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 2-methylbenzimidazole for 1*H*-2-methylimidazo[4,5-*c*]pyridine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.54 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.59 (s, 2H), 7.1-7.2 (m, 2H), 7.26 (d, 2H, *J* = 8.1 Hz), 7.4-7.6 (m, 4H), 7.8-7.9 (m, 3H), 8.10 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 495 (M+H)<sup>+</sup>.

**Example 125**

Preparation of 4-Methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 1-pyrrolidine carbonyl chloride for *N,N*-dimethylcarbamoyl chloride in step 2, and substituting 2-methylbenzimidazole for 1*H*-2-methylimidazo[4,5-*c*]pyridine in step 3. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.8-1.9 (m, 4H), 2.54 (s, 3H), 3.46 (s, 3H), 3.5-3.6 (m, 4H), 5.60 (s, 2H), 7.1-7.2 (complex m, 2H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.4-7.6 (m, 4H), 7.84 (d, 2H, *J* = 8.1 Hz), 7.97 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.18 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 521 (M+H)<sup>+</sup>. Anal calcd for C<sub>31</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> · 0.1 H<sub>2</sub>O · 0.4 CH<sub>2</sub>Cl<sub>2</sub>: C, 67.79; H, 5.25; N, 10.07. Found: C, 67.70; H, 5.11; N, 9.97.

**Example 126**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)pent-5-ylcarbonyl]indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methoxycarbonylindole for 4-chloroindole, and 6-bromohexanoyl chloride for 4-bromomethylbenzoyl chloride. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.3-1.4 (m, 2H), 1.66 (quint, 2H, *J* = 7.5 Hz), 1.77 (quint, 2H, *J* = 7.5 Hz), 2.58 (s, 3H), 2.88 (t, 2H, *J* = 7.2 Hz), 3.04 (s, 6H), 3.70 (s, 3H), 4.21 (t, 2H, *J* = 7.2 Hz), 7.40-7.45 (m, 2H), 7.56 (dd, 1H, *J* = 5.2, 1.1 Hz), 7.8-7.8 (m, 1H), 8.25 (d, 1H, *J* = 5.7 Hz), 8.59 (s, 1H), 8.79 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 476 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O: C, 64.45; H, 6.24; N, 14.45. Found: C, 64.41; H, 5.99; N, 14.20.

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**Example 127**

Preparation of 1-*N,N*-Dimethylcarbamoylmethyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl]indole.

The desired compound was prepared according to the method of Example 109, except substituting 2-chloro-*N,N*-dimethylacetamide for *N,N*-dimethylcarbamoyl chloride in step 2, and 4-methoxycarbonylindole for 4-chloroindole in step 3. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 2.84 (s, 3H), 3.08 (s, 3H), 3.58 (s, 3H), 5.30 (s, 2H), 5.64 (s, 2H), 7.25-7.45 (m, 4H), 7.6-7.7 (m, 2H), 7.78 (apparent d, 2H, *J* = 8.1 Hz), 7.86 (s, 1H), 8.31 (d, 1H, *J* = 5.4 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 510 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O: C, 64.91; H, 5.64; N, 13.05. Found: C, 64.75; H, 5.64; N, 13.05.

**Example 128**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl]indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-methoxycarbonylindole for 4-chloroindole, and 5-iodopentanoyl chloride for 4-bromomethylbenzoyl chloride. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.59-1.70 (m, 2H), 1.75-1.85 (m, 2H), 2.60 (s, 3H), 2.95 (t, 2H, *J* = 9 Hz), 3.04 (s, 3H), 3.60 (s, 3H), 4.28 (t, 2H, *J* = 9 Hz), 7.42 (d, 2H, *J* = 6 Hz), 7.62 (d, 1H, *J* = 6 Hz), 7.74-7.80 (m, 1H), 8.26 (d, 1H, *J* = 6 Hz), 8.60 (s, 1H), 8.80 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 462 (M<sup>+</sup>). Anal calcd for C<sub>25</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> · 1.0 H<sub>2</sub>O: C, 62.63; H, 6.16; N, 14.00. Found: C, 62.61; H, 6.09; N, 14.60.

**Example 129**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(2-methyl-4-(3*H*)quinazolinone-3-yl)methyl]benzoyl}indole.

Step 1: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 109, steps 1 and 2, except substituting 4-carboxymethylcarbonylindole for 4-chloroindole.

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(2-methyl-4-(3*H*)quinazolinone-3-yl)methyl]benzoyl}indole.

To a solution of 2-methyl-4-(3*H*)quinazolinone (120 mg, 0.75 mmol) in DMF (2 mL) was added lithium hexamethyldisilazide (1.0 M in THF, 0.83 mL, 0.83 mmol)

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and a solution in DMF (2 mL) of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole (300 mg, 0.75 mmol), prepared as in step 1, and LiBr (65 mg). The clear-brown solution was stirred for 20 hours at ambient temperature and then was partitioned between saturated aqueous NH<sub>4</sub>Cl and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed three times with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (10%, then 20% acetone/CH<sub>2</sub>Cl<sub>2</sub>) and reverse phase HPLC (30-65% CH<sub>3</sub>CN, H<sub>2</sub>O with 0.1% trifluoroacetic acid) gave 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(2-methyl-4(3H)quinazolinone-3-yl)methyl]benzoyl}indole (203 mg). <sup>1</sup>H NMR (DMS)-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.03 (s, 6H), 3.51 (s, 3H), 5.49 (s, 2H), 7.37 (d, 2H, J = 8.1 Hz), 7.4-7.6 (m, 3H), 7.65 (d, 1H, J = 8.1 Hz), 7.8-7.9 (m, 2H), 7.87 (d, 2H, J = 8.1 Hz), 8.15 (s, 1H), 8.1-8.2 (m, 1H). MS (DCI/NH<sub>3</sub>) m/e 523 (M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub> · 0.3 CH<sub>2</sub>Cl<sub>2</sub>: C, 66.41; H, 4.89; N, 10.22. Found: C, 66.32; H, 4.97, N, 9.73.

### Example 130

#### Preparation of 1-(2-Ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution in 1:1 THF, DMF (30 mL) of 4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (0.13 g, 0.31 mmol), prepared as in Example 115, was added NaH (95%, 9.3 mg, 0.37 mmol) and the reaction mixture was stirred for 15 minutes. Neat 2-bromoethyl ethyl ether (90%, 87 μL, 0.80 mmol) was added and stirring was continued for 48 hours. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted twice with ethyl acetate. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel gave 1-(2-ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (83 mg) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.95 (t, 3H, J = 7.5 Hz), 2.58 (s, 3H), 3.35 (q, 2H, J = 6 Hz), 3.55 (s, 3H), 3.68 (t, 2H, J = 6 Hz), 4.45 (t, 2H, J = 6 Hz), 5.65 (s, 2H), 7.28(d, 2H, J = 9 Hz), 7.34-7.45 (m, 2H), 7.63 (dd, 1H, J = 2, 6 Hz), 7.80 (d, 2H, J = 9 Hz), 7.85 (dd, 1H, J = 2, 8 Hz), 7.94 (s, 1H), 8.33 (d, 1H, J = 6 Hz), 8.87(s,1H). MS (DCI/NH<sub>3</sub>) m/e 497 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O: C, 68.89; H, 5.78; N, 11.08. Found: C, 68.97; H, 5.64; N, 10.82.

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**Example 131**

Preparation of 1-*N,N*-Dimethylsulfamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting *N,N*-dimethylsulfamoyl chloride for 2-bromoethyl ethyl ether. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 2.88 (s, 6H), 3.44 (s, 3H), 5.65 (s, 2H), 7.28 (d, 2H, J = 9 Hz), 7.53 (d, 1H, J = 9 Hz), 7.60 (d, 1H, J = 6 Hz), 7.68 (d, 1H, J = 8 Hz), 7.85 (d, 2H, J = 9 Hz), 8.08(s, 1H), 8.20 (d, 1H, J = 8 Hz), 8.30 (d, 1H, J = 6 Hz), 8.87(s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 532 (M<sup>+</sup>). Anal calcd for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>S · 0.25 H<sub>2</sub>O: C, 60.49; H, 4.79; N, 13.06. Found: C, 60.69; H, 5.09; N, 12.87.

**Example 132**

Preparation of 1-*iso*-Propyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting 1-iodo-2-methylpropane for 2-bromoethyl ethyl ether. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 0.84 (d, 6H, J = 6 Hz), 2.08-2.2 (m, 1H), 2.60 (s, 3H), 3.54 (s, 3H), 4.13 (d, 2H, J = 7 Hz), 5.63 (s, 2H), 7.28 (d, 2H, J = 9 Hz), 7.3-7.45 (m, 2H), 7.63 (d, 1H, J = 6 Hz), 7.80 (d, 2H, J = 9 Hz), 7.85 (d, 1H, J = 9 Hz), 7.98 (s, 1H), 8.33 (d, 1H, J = 6 Hz), 8.87(s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 481 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub> · 0.75 H<sub>2</sub>O: C, 70.49; H, 6.01; N, 11.33. Found: C, 70.48; H, 5.85; N, 11.54.

**Example 133**

Preparation of 1-Methoxycarbonylmethyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting methyl bromoacetate for 2-bromoethyl ethyl ether. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 3.55 (s, 3H), 3.68 (s, 3H), 5.30 (s, 2H), 5.65 (s, 2H), 7.28 (d, 1H, J = 9 Hz), 7.31-7.40 (m, 1H), 7.45 (d, 1H, J = 9 Hz), 7.62 (d, 1H, J = 6 Hz), 7.77-7.81(m, 3H), 7.99 (s, 1H), 8.31 (d, 1H, J = 6 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 497 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub> · 0.25 H<sub>2</sub>O: C, 67.12; H, 4.92; N, 11.18. Found: C, 67.17; H, 5.05; N, 10.79.

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**Example 134**

Preparation of 1-(2-Propanesulfonyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting 2-propanesulfonyl chloride for 2-bromoethyl ethyl ether. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.25 (d, 6H, J = 6 Hz), 2.58 (s, 3H), 3.43 (s, 3H), 3.97-4.08 (m, 1H), 5.65 (s, 2H), 7.28 (d, 2H, J = 9 Hz), 7.55-7.60 (m, 2H), 7.70 (d, 1H, J = 8 Hz), 7.84 (d, 2H, J = 9 Hz), 8.04 (s, 1H), 8.18 (d, 1H, J = 9 Hz), 8.30 (d, 1H, J = 6 Hz), 8.88 (s, 1H). MS (DCI/NH<sub>3</sub>) 531 (M<sup>+</sup>). Anal calcd for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>S · 0.5 H<sub>2</sub>O: C, 62.32; H, 5.04; N, 10.38. Found: C, 62.55; H, 5.02; N, 10.12.

**Example 135**

Preparation of 1-(1-Pinacolyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting 1-chloropinacolone for 2-bromoethyl ethyl ether. mp 122-127 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.23 (s, 9H), 2.60 (s, 3H), 3.58 (s, 3H), 5.57 (s, 2H), 5.65 (s, 2H), 7.30 (d, 2H, J = 9 Hz), 7.35 (d, 1H, J = 9 Hz), 7.43 (d, 1H, J = 6 Hz), 7.54 (d, 1H, J = 9 Hz), 7.62 (d, 1H, J = 6 Hz), 7.80 (d, 2H, J = 9 Hz), 7.88 (s, 1H), 8.30 (bs, 1H), 8.87 (bs, 1H). MS (DCI/NH<sub>3</sub>) m/e 523 (M<sup>+</sup>). Anal calcd for C<sub>31</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> · 0.75 H<sub>2</sub>O: C, 69.45; H, 5.92; N, 10.45. Found: C, 69.45; H, 6.17; N, 10.14.

**Example 136**

Preparation of 1-Carbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 1-(4-Nitrophenoxy carbonyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared by addition of NaH and 4-nitrophenyl chloroformate to a solution in DMF of 4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 115.

Step 2: 1-Carbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Liquid ammonia (10 drops) was condensed into a -78 °C solution in THF (12 mL) of 1-(4-nitrophenoxy carbonyl)-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (259 mg), prepared as in step

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1. The resulting clear-yellow solution was stirred for 20 minutes at -78 °C, then saturated aqueous NH<sub>4</sub>Cl was added and the reaction mixture was warmed to ambient temperature and extracted with ethyl acetate. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 32 mg of 1-carbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.58 (s, 3H), 3.45 (s, 3H), 5.65 (s, 2H), 7.29 (d, 2H, J = 9 Hz), 7.45 (t, 1H, J = 9 Hz), 7.58 (t, 2H, J = 6 Hz), 8.3-7.9 (m, 4H), 8.3 (d, 1H, J = 6 Hz), 8.34 (s, 1H), 8.55 (dd, 1H, J = 3, 9 Hz), 8.86 (s, 1H). MS (FAB) m/e 468 (M+H)<sup>+</sup>.

### Example 137

Preparation of 1-N-Methylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 136, except substituting methylamine for ammonia. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 2.82 (d, 3H, J = 6 Hz), 3.46 (s, 3H), 5.65 (s, 2H), 7.30 (d, 2H, J = 9 Hz), 7.48 (t, 1H, J = 9 Hz), 7.59 (dd, 1H, J = 3, 9 Hz), 7.61 (d, 1H, J = 6 Hz), 7.87 (d, 2H, J = 9 Hz), 8.28 (s, 1H), 8.31 (d, 1H, J = 6 Hz), 8.44 (d, 1H, J = 6 Hz), 8.52 (dd, 1H, J = 3, 9 Hz), 8.90 (bs, 1H). MS (DCI/NH<sub>3</sub>) m/e 425.

### Example 138

Preparation of 1-(2-Ethoxyethyl)-4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 4-Chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 90, except substituting 4-chloroindole for 4,7-dimethoxycarbonylindole.

Step 2: 1-(2-Ethoxyethyl)-4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 130, except substituting 4-chloro-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole, prepared as in step 1, for 4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.95 (t, 3H, J = 9 Hz), 2.57 (s, 3H), 3.2-3.3 (m, 2H), 3.68 (t, 2H, J = 6 Hz), 4.4 (t, 2H, J = 6 Hz), 5.65 (s, 2H), 7.2-7.31 (m, 4H), 7.6 (d, 1H, J = 6 Hz),

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7.65 (d, 1H, J = 9 Hz), 7.8 (d, 2H, J = 9 Hz), 7.84 (s, 1H), 8.3 (d, 1H, J = 6 Hz), 7.86 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 473 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>2</sub> · 0.75 H<sub>2</sub>O: C, 66.66; H, 5.49; N, 11.51. Found: C, 66.95; H, 5.33; N, 11.60.

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**Example 139**

Preparation of 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 96, except substituting 3-methoxy-4-bromomethylbenzoic acid for 4-chloromethylbenzoic acid. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>, then 2% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-N,N-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (120 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.84 (s, 1H), 8.28-8.26 (d, 1H, J = 5.5 Hz), 8.17 (s, 1H), 7.87-7.85 (d, 1H, J = 8.1 Hz), 7.57-7.51 (m, 3H), 7.48-7.45 (d, 1H, J = 8.1 Hz), 7.41-7.38 (d, 1H, J = 7.4 Hz), 5.52 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 3.03 (s, 6H), 2.57 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 526 (M+H)<sup>+</sup>. IR (KBr) 3450, 1700, 1395, 1320, 1300, 1200, 750 cm<sup>-1</sup>. Anal calcd for C<sub>29</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub> · 1.0 H<sub>2</sub>O: C, 64.07; H, 5.37; N, 12.88. Found: C, 63.91; H, 5.30; N, 12.59.

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**Example 140**

Preparation of 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound (230 mg) was isolated from the chromatography described in Example 139. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.80 (s, 1H), 8.29-8.27 (d, 1H, J = 5.5 Hz), 8.17 (s, 1H), 7.88-7.85 (d, 1H, J = 8.5 Hz), 7.56-7.51 (t, 1H, J = 5.4 Hz), 7.48-7.45 (d, 1H, J = 5.4 Hz), 7.43-7.41 (d, 1H, J = 7.5 Hz), 5.58 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 3.03 (s, 6H), 2.60 (s, 3H). MS (DCI/NH<sub>3</sub>) m/e 526 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub> · 0.25 H<sub>2</sub>O: C, 65.71; H, 5.22; N, 13.21. Found: C, 65.95; H, 5.15; N, 13.53.

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**Example 141**

Preparation of 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylsulfonyl}indole.  
Step 1: 3-(4-Methylthiophenyl)-4-methoxycarbonylindole.

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The desired compound was prepared according to the method of Example 57, step 1, except substituting 4-methoxycarbonylindole for indole.



Step 2: 1-*N,N*-Dimethylcarbamoyl-3-(4-methylthiophenyl)-4-methoxycarbonylindole.

The desired compound was prepared by reaction of 3-(4-methylthiophenyl)-4-methoxycarbonylindole with KOH and *N,N*-dimethylcarbamoyl chloride as described in Example 2.

Step 3: 1-*N,N*-Dimethylcarbamoyl-3-(4-methylphenylsulfonyl)-4-methoxycarbonylindole.

To a solution in acetic acid (50 mL) of 1-*N,N*-dimethylcarbamoyl-3-(4-methylthiophenyl)-4-methoxycarbonylindole (3.5 g, 9.5 mmol), prepared as in step 2, was added OXONE (potassium peroxymonosulfate, 6.2 g, 10 mmol) and the reaction mixture was stirred for 14 hours at ambient temperature. NaIO<sub>4</sub> (1.5 g) was added and the reaction was stirred for 4 hours and then quenched with saturated aqueous Na<sub>2</sub>SO<sub>3</sub>. Solid Na<sub>2</sub>SO<sub>3</sub> was added to the reddish reaction mixture until it remained bright yellow in color. The reaction mixture was diluted with H<sub>2</sub>O, made basic with saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (3%, then 20% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1.2 g of impure material which was chromatographed again (CH<sub>2</sub>Cl<sub>2</sub>) to give 1-*N,N*-dimethylcarbamoyl-3-(4-methylphenylsulfonyl)-4-methoxycarbonylindole (0.52 g).

Step 4: 1-*N,N*-Dimethylcarbamoyl-3-[(4-bromomethyl)phenylsulfonyl]-4-methoxycarbonylindole.

To a solution in CCl<sub>4</sub> (50 mL) of 1-*N,N*-dimethylcarbamoyl-3-(4-methylphenylsulfonyl)-4-methoxycarbonylindole (1.9 g, 4.7 mmol), prepared as in step 3, was added *N*-bromosuccinimide (0.85 g, 4.8 mmol) and catalytic benzoyl peroxide. The reaction mixture was stirred at reflux for 14 hours, then cooled to ambient temperature and concentrated *in vacuo*. Chromatography on silica gel (1%, then 3% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-3-[(4-bromomethyl)phenylsulfonyl]-4-methoxycarbonylindole (1.5 g) of sufficient purity to use in the next step.

Step 5: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

The desired compound was prepared according to the method of Example 90, step 3, except substituting 1-*N,N*-dimethylcarbamoyl-3-[(4-bromomethyl)phenylsulfonyl]-4-methoxycarbonylindole, prepared as in step 4, for 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole. Chromatography on silica gel (1%, then 2% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole (180 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 8.83 (s, 1H), 8.56 (s, 1H), 8.27-8.25 (d, 1H, *J* = 5.5 Hz), 7.88-7.83 (m, 4H), 7.54-7.52 (d, 1H, *J* = 5.5 Hz), 7.47-7.45 (d, 2H, *J* = 5.1 Hz), 7.31-7.28 (d, 2H, *J* = 8.5 Hz), 5.63 (s, 2H), 3.51 (s, 3H), 3.02 (s, 6H), 2.56 (s, 3H). MS (DCI/NH<sub>3</sub>) *m/e* 532 (M+H)<sup>+</sup>. IR (KBr) 3950, 1700, 1600, 1400, 1290 cm<sup>-1</sup>. Anal calcd for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>S · 1.75 H<sub>2</sub>O: C, 57.13; H, 5.14; N, 12.33. Found: C, 57.09; H, 4.63; N, 11.76.

**Example 142**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole.

The desired compound (130 mg) was isolated from the chromatography described in Example 141. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 8.56 (s, 1H), 8.29-8.27 (d, 1H, *J* = 5.8 Hz), 7.89-7.86 (d, 1H, *J* = 8.5 Hz), 7.84-7.81 (d, 1H, *J* = 5.5 Hz), 7.56-7.54 (d, 1H, *J* = 5.5 Hz), 7.48-7.45 (d, 2H, *J* = 8.0 Hz), 7.36-7.33 (d, 2H, *J* = 8.5 Hz), 5.69 (s, 2H), 3.51 (s, 3H), 3.02 (s, 6H), 2.56 (s, 3H). MS (DCI/NH<sub>3</sub>) *m/e* 532 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>S · 1.75 H<sub>2</sub>O: C, 57.59; H, 5.10; N, 12.43. Found: C, 57.57; H, 4.75; N, 13.05.

**Example 143**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared by catalytic hydrogenolysis (1 atm. H<sub>2</sub>, 10% palladium on carbon, ethanol) of 1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 107. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.02 (t, 3H, *J* = 9 Hz), 2.58 (s, 3H), 2.98 (bs, 8H), 5.65 (s, 2H), 7.13 (d, 1H, *J* = 9 Hz), 7.28-7.33 (m, 3H), 7.47 (d, 1H, *J* = 9 Hz), 7.60 (d, 1H, *J* = 6 Hz), 7.85-7.90 (m, 3H), 8.30 (m, 3H), 8.86

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(s, 1H). MS (DCI/NH<sub>3</sub>) m/e 466 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub> · 0.75 H<sub>2</sub>O: C, 70.54; H, 6.03; N, 14.27. Found: C, 70.20; H, 5.99; N, 14.61.

#### Example 144

5 Preparation of 1-*N,N*-Dimethylcarbamoyl-4-hydroxy-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at -78 °C of 1-*N,N*-dimethylcarbamoyl-4-methoxy-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (94 mg, 0.20 mmol), prepared as in Example 121, was added BBr<sub>3</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 10 240 µL, 0.24 mmol), and the reaction mixture was stirred for 30 minutes at -78 °C. The cold bath was removed and the reaction mixture was stirred overnight at ambient temperature. The reaction was quenched by addition of H<sub>2</sub>O (5 mL) and the resulting slightly turbid yellow solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The 15 resulting yellow solid was dissolved in acetone (15 mL) and aqueous 1 M HCl (5 mL) was added. The solution was shaken for 5-10 minutes, neutralized with saturated aqueous NaHCO<sub>3</sub>, and extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-dimethylcarbamoyl-4-hydroxy-3-{4-[(1H-2-methylimidazo[4.5- 20 c]pyrid-1-yl)methyl]benzoyl}indole (48 mg) as an amorphous yellow solid. mp 99-108 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 2.98 (s, 6H), 5.68 (s, 2H), 6.68 (d, 1H, J = 9 Hz), 7.03 (d, 1H, J = 9 Hz), 7.25 (d, 1H, J = 9 Hz), 7.28-7.36 (m, 2H), 7.64 (d, 1H, J = 6 Hz), 7.86 (d, 2H, J = 9Hz), 8.15 (s, 1H), 8.34 (bs, 1H), 8.88 (bs, 1H). MS (DCI/NH<sub>3</sub>) m/e 454 (M<sup>+</sup>).

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#### Example 145

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

30 Step 1: 1-*N,N*-Dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-(4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 102, steps 1-4, except substituting 6-bromo-4-methoxycarbonylindole for 4-bromoindole.

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Step 2: 1-*N,N*-Dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-(4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl)indole.

The desired compound was prepared by catalytic hydrogenolysis (4 atm H<sub>2</sub>, Raney nickel, THF) of 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-(4-(*N*-3-nitropyridin-4-yl)aminomethylbenzoyl)indole, prepared as in step 1.

Step 3: 1-*N,N*-Dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared by heating a solution of 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-(4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl)indole (2.53 g), prepared as in step 2, in acetic acid (20 mL) and acetic anhydride (20 mL) as described in Example 57, step 8. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 3.01 (s, 6H), 3.50 (s, 3H), 5.64 (s, 2H), 7.28 (d, 2H, J = 8.4 Hz), 7.59 (dd, 1H, J = 5.7, 0.6 Hz), 7.67 (d, 1H, J = 2.1 Hz), 7.84 (d, 2H, J = 8.4 Hz), 8.07 (d, 1H, J = 2.1 Hz), 8.17 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 576 (M+H)<sup>+</sup>, 574. Anal calcd for C<sub>28</sub>H<sub>24</sub>N<sub>5</sub>O<sub>4</sub>Br · 0.4 ethyl acetate: C, 58.31; H, 4.50; N, 11.49. Found: C, 58.44; H, 4.35; N, 11.21.

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### Example 146

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(benzo[b]fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 105, except substituting 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 145, for 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 3.07 (s, 6H), 3.53 (s, 3H), 5.66 (s, 2H), 7.29 (t, 1H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.7 Hz), 7.35 (t, 1H, J = 8.4 Hz), 7.62 (d, 1H, J = 5.4 Hz), 7.63 (s, 1H), 7.67 (d, 1H, J = 8.4 Hz), 7.69 (d, 1H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.7 Hz), 8.11 (d, 1H, J = 1.5 Hz), 8.23 (s, 1H), 8.32 (d, 1H, J = 5.4 Hz), 8.35 (d, 1H, J = 1.5 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 612 (M+H)<sup>+</sup>. Anal calcd for C<sub>36</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub> · 0.4 ethyl acetate · 0.4 H<sub>2</sub>O: C, 69.04; H, 5.08; N, 10.71. Found: C, 69.25; H, 4.94; N, 10.69.

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**Example 147**

Preparation of 1-*N,N*-Dimethylcarbamoyl-6-(fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 104, except substituting 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, prepared as in Example 145, for 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.58 (s, 3H), 3.06 (s, 6H), 3.51 (s, 3H), 5.65 (s, 2H), 6.63 (dd, 1H, *J* = 2.4, 3.6 Hz), 7.11 (d, 1H, *J* = 3.6 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 1H, *J* = 6.3 Hz), 7.79 (d, 1H, *J* = 1.2 Hz), 7.87 (d, 2H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 1.2 Hz), 8.10 (d, 1H, *J* = 2.4 Hz), 8.14 (s, 1H), 8.30 (d, 1H, *J* = 6.3 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 562 (M+H)<sup>+</sup>. Anal calcd for C<sub>32</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub> · 0.5 ethyl acetate · 0.1 H<sub>2</sub>O: C, 67.23; H, 5.18; N, 11.53. Found: C, 67.24; H, 5.03; N, 11.57.

**Example 148**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

Step 1: 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)indole.

The desired compound was prepared by treating 4-hydroxyindole with 2 equivalents of NaH and 2 equivalents of dimethylcarbamyl chloride according to the method of Example 130.

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 4, step 2, except substituting 1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)indole, prepared as in step 1, for 6-(4-fluorophenyl)indole-1-carboxylic acid diamide.

Step 3: 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 102, steps 2-5, except substituting 1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-(4-chloromethylbenzoyl)indole, prepared as in step 2, for 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR

(DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  2.58 (s, 3H), 2.70 (s, 3H), 2.85 (s, 3H), 3.0 (s, 6H), 5.65 (s, 2H), 6.96 (d, 1H, J = 8 Hz), 7.28 (d, 2H, J = 9 Hz), 7.30-7.38 (m, 1H), 7.50 (d, 1H, J = 9 Hz), 7.60 (d, 1H, J = 6 Hz), 7.80 (d, 2H, J = 9 Hz), 7.94 (s, 1H), 8.30 (d, 1H, J = 6 Hz), 8.87 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 525 (M<sup>+</sup>). Anal calcd for C<sub>29</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> · 1.0 H<sub>2</sub>O: C, 64.19; H, 5.57; N, 15.48. Found: C, 64.40; H, 5.33; N, 15.38.

### Example 149

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

10 Step 1: 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)indole.

To a solution of 4-aminoindole (1.0 g, 7.6 mmol) in THF (30 mL) at -78 °C was added lithium hexamethyldisilazide (1.0 M in THF, 7.6 mL, 7.6 mmol). The reaction mixture was stirred for 5 minutes at -78 °C and *N,N*-dimethylcarbamyl chloride (0.74 mL, 8.0 mmol) was added. The cold bath was removed and the reaction mixture was stirred for 80 minutes. The reaction mixture was cooled back to -78 °C and lithium hexamethyldisilazide (1.0 M in THF, 7.6 mL, 7.6 mmol) was added. The reaction mixture was stirred for 10 minutes at -78 °C and *N,N*-dimethylcarbamyl chloride (0.74 mL, 8.0 mmol) was added. The reaction mixture was stirred for 15 minutes at -78 °C, the cold bath was removed and the reaction mixture was warmed to ambient temperature. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (ethyl acetate) gave 1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)indole (0.96 g).

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Step 2: 1-*N,N*-Dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 4, steps 2 and 3, except substituting 1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)indole, prepared as in step 1, for 6-(4-fluorophenyl)indole -1-carboxylic acid diamide. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  2.58 (s, 3H), 2.93 (s, 6H), 3.00 (s, 6H), 5.63 (s, 2H), 7.13 (d, 1H, J = 6 Hz), 7.28-7.33 (m, 3H), 7.60 (d, 1H, J = 3 Hz), 7.83 (d, 2H, J = 6 Hz), 7.97 (s, 1H), 8.03 (d, 1H, J = 6 Hz), 8.30 (d, 1H, J = 3 Hz), 8.85 (s, 1H), 10.34 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 524 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>29</sub>N<sub>7</sub>O<sub>3</sub> · 1.75 H<sub>2</sub>O: C, 62.74; H, 5.90; N, 17.66. Found: C, 62.70; H, 5.57; N, 16.04.

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**Example 150**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-cyano-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride.

5    Step 1: 1*H*-1-(4-Bromobenzyl)-2-methylimidazo[4.5-*c*]pyridine.

The desired compound was prepared according to the method of Example 57, steps 7 and 8, except substituting 4-bromobenzylamine for 1-phenylsulfonyl-3-[(4-aminomethyl)phenylsulfonyl]indole.

10   Step 2: 1*H*-1-(4-Trimethylstannylbenzyl)-2-methylimidazo[4.5-*c*]pyridine.

To a solution under N<sub>2</sub> of 1*H*-1-(4-bromobenzyl)-2-methylimidazo[4.5-*c*]pyridine (3.48 g, 11.5 mmol), prepared as in step 1, and hexamethylditin (7.73 g, 23.6 mmol) in dimethoxyethane (150 mL) was added tetrakis(triphenylphosphine) palladium(0) (660 mg, 0.57 mmol) and the reaction mixture was stirred at reflux for  
15   3.5 hours. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was concentrated *in vacuo* and taken up in ethyl acetate. The ethyl acetate solution was washed twice with pH 7 buffer and once with brine. The combined aqueous washings were extracted twice with ethyl acetate. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*.  
20   Chromatography on silica gel (4% methanol/CHCl<sub>3</sub>) followed by trituration with hexane gave 1*H*-1-(4-trimethylstannylbenzyl)-2-methylimidazo[4.5-*c*]pyridine (3.74 g) as soft crystals, mp 123-126 °C.

25   Step 3: 1-*N,N*-Dimethylcarbamoyl-4-cyano-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride.

To a solution of 1-*N,N*-dimethylcarbamoyl-4-cyanoindole-3-carbonyl chloride (prepared by treatment of 566 mg of 1-*N,N*-dimethylcarbamoyl-4-cyanoindole-3-carboxylic acid with thionyl chloride) in THF (20 mL) was added allylpalladium chloride dimer (52 mg, 0.14 mmol) and 1*H*-1-(4-trimethylstannylbenzyl)-2-  
30   methylimidazo[4.5-*c*]pyridine (850 mg, 2.2 mmol), prepared as in step 2. The reaction mixture was heated at reflux for 4 hours, and then was cooled to ambient temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and filtered. The filtrate was washed with 5% aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. The combined aqueous washings were extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and  
35   concentrated *in vacuo*. The crude material was chromatographed three times (twice with 4-8% methanol/CHCl<sub>3</sub>; then 7% methanol/CH<sub>2</sub>Cl<sub>2</sub>). The material obtained after

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the chromatographies was dissolved in THF (3 mL) and 2 drops of 4 N HCl/dioxane was added. The resulting fine solid was filtered and washed with ether to give 1-*N,N*-dimethylcarbamoyl-4-cyano-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride (13 mg). mp 179-181 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.70 (s, 3H), 3.01 (s, 6H), 5.88 (s, 2H), 7.39 (d, 2H, *J* = 8.1 Hz), 7.56 (t, 1H, *J* = 8.1 Hz), 7.84 (dd, 1H, *J* = 8.1, 1.2 Hz), 7.94 (d, 2H, *J* = 8.1 Hz), 8.02 (dd, 1H, *J* = 8.1, 1.2 Hz), 8.27 (s, 1H), 8.32 (d, 1H, *J* = 6.3 Hz), 8.68 (d, 1H, *J* = 6.3 Hz), 9.44 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 463 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub>Cl · 1.4 H<sub>2</sub>O: C, 61.87; H, 4.96; N, 16.03. Found: C, 61.89; H, 4.84; N, 16.00.

### Example 151

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzyl}indole.

Step 1: 4-Methoxycarbonyl-3-[(4-chloromethyl)benzyl]indole.

To a 0 °C solution of trifluoroacetic acid (0.65 mL, 8.6 mmol) and triethylsilane (2.7 mL, 17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (17 mL) was added dropwise a solution of 4-methoxycarbonylindole (1.0 g, 5.7 mmol) and 4-chloromethylbenzaldehyde (0.97 g, 6.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (29 mL). The reaction mixture was stirred for 1 hour at 0 °C and 20 hours at ambient temperature and then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (25% hexane/CH<sub>2</sub>Cl<sub>2</sub>, then CH<sub>2</sub>Cl<sub>2</sub>) gave 4-methoxycarbonyl-3-[(4-chloromethyl)benzyl]indole (1.06 g).

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[(4-chloromethyl)benzyl]indole.

The desired compound was prepared according to the method of Example 130, except substituting 4-methoxycarbonyl-3-[(4-chloromethyl)benzyl]indole, prepared as in step 1, for 4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, and substituting *N,N*-dimethylcarbamyl chloride for 2-bromoethyl ethyl ether.



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Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzyl}indole.

The desired compound was prepared according to the method of Example 90, step 3, except substituting 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(4-chloromethyl)benzyl]indole, prepared as in step 2, for 4,7-dimethoxycarbonyl-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.00 (s, 6H), 3.56 (s, 3H), 4.13 (s, 2H), 5.43 (s, 2H), 7.03 (s, 4H), 7.2-7.3 (m, 1H), 7.43 (dd, 1H, *J* = 7.5, 1.2 Hz), 7.50-7.55 (m, 2H), 7.83 (dd, 1H, *J* = 8.1, 1.2 Hz), 8.25 (d, 1H, *J* = 5.4 Hz), 8.81 (d, 1H, *J* = 1.2 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 482 (M+H)<sup>+</sup>.

### Example 152

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 1*H*-2-methylimidazo[4,5-*b*]pyridine, prepared as is Example 27, step 1, for 1*H*-2-methylimidazo[4,5-*c*]pyridine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.00 (s, 3H), 5.65 (s, 2H), 7.18-7.22 (m, 1H), 7.25-7.40 (m, 4H), 7.65 (d, 1H, *J* = 9 Hz), 7.86 (d, 2H, *J* = 9 Hz), 7.93 (d, 1H, *J* = 9 Hz), 8.05 (s, 1H), 8.35 (d, 1H, *J* = 6 Hz). MS (DCI/NH<sub>3</sub>) 472 (M<sup>+</sup>).

### Example 153

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*b*]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 43, except substituting 1*H*-2-methylimidazo[4,5-*b*]pyridine, prepared as is Example 27, step 1, for 1*H*-2-methylimidazo[4,5-*c*]pyridine. 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*b*]pyrid-3-yl)methyl]benzoyl}indole (286 mg) was isolated by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>, then 2%, then 4%, then 5% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.55 (s, 3H), 3.02 (s, 6H), 3.48 (s, 3H), 5.62 (s, 2H), 7.27 (dd, 1H, *J* = 8.1, 4.8 Hz), 7.34 (apparent d, 2H, *J* = 8.1 Hz), 7.4-7.5 (m, 1H), 7.56 (dd, 1H, *J* = 7.2, 1.2 Hz), 7.85 (apparent d, 2H, *J* = 8.4 Hz), 7.86 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.00 (dd, 1H, *J* = 8.1, 1.5 Hz), 8.12 (s, 1H), 8.31 (dd, 1H, *J* = 5.1, 1.5 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 496 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> · 0.8 H<sub>2</sub>O: C, 65.95; H, 5.26; N, 13.73. Found: C, 65.63; H, 4.86; N, 13.47.

**Example 154**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound (45 mg) was isolated from the chromatography described in Example 153. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.59 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.65 (s, 2H), 7.21 (dd, 1H, *J* = 8.1, 4.8 Hz), 7.29 (apparent d, 2H, *J* = 8.1 Hz), 7.4-7.5 (m, 1H), 7.57 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.85 (apparent d, 2H, *J* = 8.4 Hz), 7.86 (dd, 1H, *J* = 8.1, 1.2 Hz), 7.95 (dd, 1H, *J* = 8.1, 1.5 Hz), 8.11 (s, 1H), 8.36 (dd, 1H, *J* = 4.8, 1.5 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 496 (M+H)<sup>+</sup>.  
Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> · 1.0 H<sub>2</sub>O: C, 65.49; H, 5.30; N, 13.64. Found: C, 65.45; H, 5.06; N, 13.50.

**Example 155**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 43. 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl]benzoyl}indole (143 mg) was isolated by chromatography on silica gel (5%, then 10%, then 12% methanol/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  2.51 (s, 3H), 3.02 (s, 6H), 3.46 (s, 3H), 5.76 (s, 2H), 7.4-7.65 (m, 3H), 7.54 (d, 2H, *J* = 8.1 Hz), 7.87 (dd, 1H, *J* = 9.3, 1.2 Hz), 7.90 (d, 2H, *J* = 8.1 Hz), 8.13 (s, 1H), 8.18 (dd, 1H, *J* = 6.9, 1.8 Hz), 8.97 (d, 1H, *J* = 1.5 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 496 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> · 1.6 H<sub>2</sub>O: C, 64.14; H, 5.42; N, 13.36. Found: C, 64.17; H, 5.03; N, 13.36.

**Example 156**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)eth-1-yl]benzoyl}indole.

Step 1: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-(4-acetylbenzoyl)indole.

To a solution in dichloroethane (10 mL) of 4-acetylbenzoyl chloride (3.0 mmol), prepared by treatment of 4-acetylbenzoic acid with oxalyl chloride, was added AlCl<sub>3</sub> (1.2 g, 9.0 mmol) and the brown solution was heated at 50 °C for 10 minutes. 1-*N,N*-dimethoxycarbonyl-4-methoxycarbonylindole (738 mg, 3.0 mmol) was added and the reaction mixture was heated at 65 °C for 8 hours. The reaction mixture was cooled to ambient temperature and poured into aqueous 3 *N* HCl. The aqueous phase was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with aqueous 1 *N* NaOH and brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in*

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*vacuo*. Chromatography on silica gel (40% to 80% ethyl acetate/hexane) gave 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(4-acetyl)benzoyl]indole (620 mg).

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-hydroxyethyl)benzoyl]indole.

To a solution in 3:1 ethanol-CH<sub>2</sub>Cl<sub>2</sub> (8 mL) of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(4-acetyl)benzoyl]indole (260 mg, 0.663 mmol), prepared as in step 1, was added NaBH<sub>4</sub> (28.2 mg, 0.742 mmol) in portions. After 5 minutes, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and concentrated *in vacuo*. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with brine. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a yellow oil (260 mg) which was used without further purification.

Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-methanesulfonyloxyethyl)benzoyl]indole.

To a 0 °C solution in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) of the 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-hydroxyethyl)benzoyl]indole prepared in step 2 (260 mg) was added triethylamine (138 µL, 0.99 mmol) and methanesulfonyl chloride (61.3 µL, 0.79 mmol) and the reaction mixture was stirred for 20 minutes. The cold bath was removed and stirring was continued for 10 minutes. The reaction mixture was poured into a mixture of brine and saturated aqueous NaHCO<sub>3</sub> and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-methanesulfonyloxyethyl)benzoyl]indole which was used without further purification.

Step 4: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-azidoethyl)benzoyl]indole.

To a solution in DMF (8 mL) of the 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-methanesulfonyloxyethyl)benzoyl]indole prepared in step 3 was added sodium azide (429 mg, 6.6 mmol) and the reaction mixture was heated at 60 °C for 1 hour. The reaction mixture was poured into brine and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*.

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Chromatography on silica gel (40-60% ethyl acetate/hexane) gave 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-azidoethyl)benzoyl]indole (250 mg).

5 Step 5: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1H-2-methylimidazo[4,5-c]pyrid-1-yl)ethyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 29, steps 5 and 6, except substituting 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-azidoethyl)benzoyl]indole, prepared as in step 4, for 1-*N,N*-dimethylcarbamoyl-3-(4-aminomethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.97 (d, 3H, J = 6.9 Hz), 2.64 (s, 3H), 3.03 (s, 6H), 3.46 (s, 3H), 6.07 (q, 1H, J = 6.9 Hz), 7.26 (dd, 1H, J = 0.9, 5.7 Hz), 7.43 (d, 2H, J = 8.1 Hz), 7.46 (t, 1H, J = 8.4 Hz), 7.58 (dd, 1H, J = 1.2, 7.5 Hz), 7.86 (d, 2H, J = 8.1 Hz), 7.88 (dd, 1H, J = 0.6, 7.5 Hz), 8.12 (s, 1H), 8.17 (d, 1H, J = 5.7 Hz), 8.83 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 511 (M+2)<sup>+</sup>, 510 (M+1)<sup>+</sup>, 378, 277, 205.

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**Example 157**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1H-imidazo[4,5-c]pyrid-1-yl)ethyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 30, except substituting 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[4-(1-(*N*-3-aminopyridin-4-yl)ethyl)benzoyl]indole, prepared as in Example 156, for 1-*N,N*-dimethylcarbamoyl-3-[4-(*N*-3-aminopyridin-4-yl)aminomethylbenzoyl]indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.3 (d, 3H, J = 6.9 Hz), 3.1 (s, 6H), 3.43 (s, 3H), 6.04 (q, 1H, J = 6.9 Hz), 7.45 (t, 1H, J = 8.4 Hz), 7.51-7.57 (m, 3H), 7.84-7.89 (m, 3H), 8.11 (s, 1H), 8.30 (d, 1H, J = 5.2 Hz), 8.79 (s, 1H), 8.99 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 496 (M+H)<sup>+</sup>, 378, 167.

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**Example 158**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

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Step 1: 5-chloro-1,2-phenylenediamine.

To a suspension in diethyl ether (50 mL) of 5-chloro-2-nitroaniline (2.70 g, 15.6 mmol) was added zinc powder (10.2 g, 156 mmol) in portions. The reaction mixture was filtered and concentrated *in vacuo* to give 5-chloro-2-aminoaniline which was used without further purification.

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Step 2: 5- and 6-Chloro-2-methylbenzimidazole.

The 5-chloro-1,2-phenylenediamine prepared in step 1 was dissolved in acetic acid (10 mL) and the solution was heated at 95 °C for 4 hours. The reaction mixture was then cooled in an ice bath and taken to pH = 8-9 with concentrated NH<sub>4</sub>OH. The resulting precipitate was filtered, washed with H<sub>2</sub>O, and dried in a vacuum oven to give a mixture of 5- and 6-chloro-2-methylbenzimidazole (2.25 g).

Step 3: 1-N, N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

Sodium hydride (60% oil dispersion, 22.5 mg, 0.563 mmol) was washed three times with hexane and suspended in DMF (3 mL). A mixture of mixture of 5- and 6-chloro-2-methylbenzimidazole (75 mg, 0.450 mmol), prepared as in step 1, was added, the reaction mixture was stirred for 5 minutes, and LiBr (20 mg) and 1-N, N-dimethylcarbamoyl-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole (150 mg, 0.373 mmol) were added. The reaction mixture was stirred for 7.5 hours at ambient temperature and then was poured into H<sub>2</sub>O and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (60% ethyl acetate/hexane, then 10% methanol/CH<sub>2</sub>Cl<sub>2</sub>), followed by HPLC (20-70% CH<sub>3</sub>CN/H<sub>2</sub>O) gave a mixture of 1-N, N-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole in about a 1:1 ratio of Cl regioisomers. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 2.54 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.27 (s, 3H), 3.28 (s, 3H), 5.62 (s, 2H), 5.62 (s, 2H), 7.18-7.22 (m, 1H), 7.18-7.22(m, 1H), 7.25 (d, 2H, J = 8.4 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.43 (t, 1H, J = 8.7 Hz), 7.43 (t, 1H, J = 8.7 Hz), 7.52-7.58 (m, 2H), 7.52-7.58 (m, 2H), 7.62 (d, 1H, J = 2.6 Hz), 7.68 (d, 1H, J = 2.6Hz), 7.82-7.88 (m, 3H), 7.82-7.88 (m, 3H), 8.09 (s, 1H), 8.10 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 529 (M+H)<sup>+</sup>, 364, 182, 167. Anal calcd for C<sub>29</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub> · 0.75 CH<sub>3</sub>OH · 0.25 CF<sub>3</sub>CO<sub>2</sub>H: C, 62.47; H, 4.89; N, 9.63. Found: C, 62.43; H, 4.86; N, 9.59.

**Example 159**

Preparation of 1-N, N-Dimethylcarbamoyl-4-chloro-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of chlorine regioisomers according to the method of Example 158, except substituting 1-N, N-dimethylcarbamoyl-4-chloro-3-(4-chloromethylbenzoyl)indole, prepared as in

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Example 109, step 2, for 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.51 (s, 3H), 2.52 (s, 3H), 3.0 (s, 6H), 3.0 (s, 6H), 5.62 (s, 2H), 5.62 (s, 2H), 7.17-7.39 (m, 0.5H), 7.17-7.39 (m, 0.5H), 7.52 (d, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.62-7.67 (m, 2H), 7.62-7.67 (m, 2H), 7.85 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz), 8.04 (s, 1H), 8.05 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 505 (M+H)<sup>+</sup>, 140, 167.

### Example 160

Preparation of 1-(2-Ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

Step 1: 1-(2-Ethoxyethyl)-4-methoxycarbonylindole.

The desired compound was prepared according to the method of Example 130, except substituting 4-methoxycarbonylindole, prepared as in Example 43, step 1, for 4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

Step 2: 1-(2-Ethoxyethyl)-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole.

The desired compound was prepared according to the method of Example 4, step 2, except substituting 1-(2-ethoxyethyl)-4-methoxycarbonylindole, prepared as in step 1, for 6-(4-fluorophenyl)indole-1-carboxylic acid dimethylamide.

Step 3: 1-(2-Ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of chlorine regioisomers according to the method of Example 158, except substituting 1-(2-ethoxyethyl)-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole, prepared as in step 2, for 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-(4-chloromethylbenzoyl)indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.97 (t, 3H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz), 2.53 (s, 3H), 2.56 (s, 3H), 3.35 (q, 2H, J = 7.4 Hz), 3.35 (q, 2H, J = 7.4 Hz), 3.55 (s, 3H), 3.56 (s, 3H), 3.69 (t, 2H, J = 5.8 Hz), 3.69 (t, 2H, J = 5.8 Hz), 4.44 (t, 2H, J = 5.8 Hz), 4.44 (t, 2H, J = 5.8 Hz), 5.61 (s, 2H), 5.61 (s, 2H), 7.18-7.27 (m, 3H), 7.18-7.27 (m, 3H), 7.33-7.43 (m, 2H), 7.33-7.43 (m, 2H), 7.57 (t, 1H, J = 8.7 Hz), 7.57 (t, 1H, J = 8.7 Hz), 7.63 (d, 1H, J = 2.4 Hz), 7.70 (d, 1H, J = 2.5 Hz), 7.80 (dd, 2H, J = 6.5, 8.8 Hz), 7.80 (dd, 2H, J = 6.5, 8.8 Hz), 7.85 (dd, 1H, J = 1.2, 8.8 Hz), 7.85 (dd, 1H, J = 1.2, 8.8 Hz), 7.92 (s, 1H), 7.93 (s, 1H). MS

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(DCI/NH<sub>3</sub>) m/e 530 (M+H)<sup>+</sup>, 365, 248, 181, 169. Anal calcd for C<sub>30</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>4</sub> · 0.475 H<sub>2</sub>O: C, 66.78; H, 5.41; N, 7.80. Found: C, 66.81; H, 5.36; N, 7.88.

### Example 161

5 Preparation of 1-(Pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[1H-2-methyl-5- and 6-chlorobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of chlorine regioisomers according to the method of Example 160, except substituting 1-pyrrolidine carbonyl chloride, for 2-bromoethyl ethyl ether. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.87 (bs, 2H), 1.87 (bs, 2H), 2.52 (s, 3H), 2.54 (s, 3H), 3.30 (s, 3H), 3.47 (s, 3H), 3.52 (bs, 2H), 3.52 (bs, 2H), 5.61 (s, 2H), 5.61 (s, 2H), 7.18-7.23 (m, 1H), 7.18-7.23 (m, 1H), 7.26 (d, 2H, J = 8.4 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.52-7.59 (m, 2H), 7.52-7.59 (m, 2H), 7.63 (d, 1H, J = 2.0 Hz), 7.68 (d, 1H, J = 2.0 Hz), 7.83 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.98 (d, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.18 (s, 1H), 8.19 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 555 (M+H)<sup>+</sup>, 169. Anal calcd for C<sub>31</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>4</sub> · 0.8 H<sub>2</sub>O · 0.2 DMF: C, 65.01; H, 5.17; N, 10.06. Found: C, 64.95; H, 4.91; N, 10.00.

### Example 162

20 Preparation of 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1H-2-(trifluoromethyl)benzimidazolyl)methyl]benzoyl}indole.

Step 1: 1H-2-(Trifluoromethyl)benzimidazole.

A mixture of 1,2-diaminobenzene (1.0 g), trifluoroacetic acid (1 mL) and trifluoroacetic anhydride (1 mL) was heated at 60 °C for 10 hours. The reaction mixture was then cooled in an ice bath and taken to pH = 7-8 with concentrated NH<sub>4</sub>OH. The resulting white solid was filtered and recrystallized from ethanol to give 400 mg of 1H-2-(trifluoromethyl)benzimidazole as colorless crystals.

30 Step 2: 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1H-2-(trifluoromethyl)benzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 158, step 3, except substituting 1H-2-(trifluoromethyl)benzimidazole, prepared as in step 1, for 5- and 6-chloro-2-methylbenzimidazole. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.11 (s, 6H), 3.53 (s, 3H), 5.61 (s, 2H), 7.17 (d, 2H, J = 8.4 Hz), 7.27-7.30 (m, 1H), 7.39-7.45 (m, 3H), 7.69 (s, 1H), 7.73 (d, 1H, J = 7.6 Hz), 7.82-7.86 (m, 3H),

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7.91-7.95 (m, 1H). MS (DCI/NH<sub>3</sub>) m/e 550 (M+2)<sup>+</sup>, 549 (M+H)<sup>+</sup>, 364, 277, 204, 187.

### Example 163

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole.

Step 1: 5- and 6-Methyl-2-methylbenzimidole.

A mixture of 3,4-diaminotoluene (1.0 g), acetic anhydride (1.5 mL) and acetic acid (2.0 mL) was heated at 85 °C for 12 hours. The reaction mixture was cooled in an ice bath and taken to pH = 8 with concentrated NH<sub>4</sub>OH. The resulting solid was filtered and dried in a vacuum oven to give 1.2 g of 5- and 6-methyl-2-methylbenzimidole as light-brown crystals.

Step 2: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of methyl regioisomers according to the method of example 158, step 3, except substituting 5- and 6-methyl-2-methylbenzimidazole, prepared as in step 1, for 5- and 6-chloro-2-methylbenzimidazole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.39 (s, 3H), 2.39 (s, 3H), 2.50 (s, 3H), 2.50 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.47 (s, 3H), 3.47 (s, 3H), 5.55 (s, 2H), 5.55 (s, 2H), 6.98-7.00 (m, 1H), 6.98-7.00 (m, 1H), 7.24 (d, 2H, J = 8.8 Hz), 7.24 (d, 2H, J = 8.8 Hz), 7.29 (s, 1H), 7.35 (s, 1H), 7.36 (d, 1H, J = 8.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.45 (t, 1H, J = 8.4 Hz), 7.45 (t, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.82 -7.88 (m, 3H), 7.82 -7.88 (m, 3H), 8.11 (s, 1H), 8.12 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 509 (M+H)<sup>+</sup>, 364.

### Example 164

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-4- and 7-methylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of methyl regioisomers according to the method of Example 163, except substituting 2,3-diaminotoluene for 3,4-diaminotoluene. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.39 (s, 3H), 2.39 (s, 3H), 2.50 (s, 3H), 2.50 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.48 (s, 3H), 3.48 (s, 3H), 5.56 (s, 2H), 5.56 (s, 2H), 6.99 (d, 1H, J = 8.6 Hz), 6.99 (d, 1H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.29 (s, 1H), 7.55 (d, 1H, J = 7.8 Hz), 7.56 (s, 1H), 7.44 (d, 1H, J = 7.9 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.82-7.88 (m, 3H),



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7.82-7.88 (m, 3H), 8.11 (s, 1H), 8.12 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 509 (M+H)<sup>+</sup>, 161. Anal calcd for C<sub>30</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> · 0.6 H<sub>2</sub>O · 0.3 EtOH; C, 68.86; H, 5.96; N, 10.49. Found: C, 68.93; H, 5.98; N, 10.17.

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**Example 165**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-fluorobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of fluorine regioisomers according to the method of Example 158, except substituting 4-fluoro-2-nitroaniline for 5-chloro-2-nitroaniline. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.51 (s, 3H), 2.54 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.48 (s, 3H), 3.48 (s, 3H), 5.59 (s, 2H), 5.61 (s, 2H), 7.02 (dt, 1H, J = 2.4, 10.2 Hz), 7.04 (dt, 1H, J = 2.4, 10.2 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.38 (dd, 1H, J = 2.7, 10.2 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.45 (dd, 1H, J = 2.7, 10.1 Hz), 7.51 (dd, 1H, J = 5.1, 9.2 Hz), 7.56 (dd, 1H, J = 5.0, 9.2 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.83-7.88 (m, 3H), 7.83-7.88 (m, 3H), 8.11 (s, 1H), 8.14 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 513 (M+H)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>25</sub>FN<sub>4</sub>O<sub>4</sub> · 0.2 H<sub>2</sub>O: C, 65.69; H, 4.89; N, 10.50. Found: C, 65.53; H, 4.89; N, 10.51.

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**Example 166**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-nitrobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of nitro regioisomers according to the method of Example 158, step 3, except substituting 5-nitro-2-methylbenzimidazole for 6-chloro-2-methylbenzimidazole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 2.61 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.46 (s, 3H), 3.47 (s, 3H), 5.73 (s, 2H), 5.80 (s, 2H), 7.29 (d, 2H, J = 8.7 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.45 (t, 1H, J = 8.7 Hz), 7.45 (t, 1H, J = 8.7 Hz), 7.55-7.58 (m, 1H), 7.55-7.58 (m, 1H), 7.78 (d, 1H, J = 8.7 Hz), 7.78 (d, 1H, J = 8.7 Hz), 7.83-7.88 (m, 3H), 7.83-7.88 (m, 3H), 8.10-8.17 (m, 2H), 8.10-8.17 (m, 2H), 8.47 (d, 1H, J = 2.6 Hz), 8.60 (d, 1H, J = 2.6 Hz). MS (DCI/NH<sub>3</sub>) m/e 540 (M+H)<sup>+</sup>, 178.

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**Example 167**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5,6-dichlorobenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 158, steps 2 and 3, except substituting 4,5-dichloro-1,2-phenylenediamine for 5-chloro-1,2-phenylenediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.52 (s, 3H), 3.02 (s, 6H), 3.48 (s, 3H), 6.63 (s, 2H), 7.25 (d, 2H, J = 8.4 Hz), 7.45 (t, 1H, J = 7.8 Hz), 7.57 (dd, 1H, J = 7.8, 0.6 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H), 7.87 (dd, 1H, J = 0.6, 7.8 Hz), 7.95 (s, 1H), 8.12 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 563 (M+H)<sup>+</sup>.

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**Example 168**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of ester regioisomers according to the method of Example 158, steps 2 and 3, except substituting methyl 3,4-diaminobenzoate for 5-chloro-1,2-phenylenediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.57 (s, 3H), 2.58 (s, 3H), 3.02 (s, 6H), 3.02 (s, 6H), 3.47 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.67 (s, 2H), 5.73 (s, 2H), 7.23 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 9.5 Hz), 7.68 (d, 1H, J = 9.5 Hz), 7.81-7.88 (m, 4H), 7.81-7.88 (m, 4H), 8.11 (s, 1H), 8.12 (s, 1H), 8.15 (d, 1H, J = 1.8 Hz), 8.18 (d, 1H, J = 1.8 Hz). MS (DCI/NH<sub>3</sub>) m/e 553 (M+H)<sup>+</sup>, 364, 191.

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**Example 169**

Preparation of 1-(Pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of ester regioisomers according to the method of Example 160, except substituting 1-pyrrolidine carbonyl chloride, for 2-bromoethyl ethyl ether in step 1, and substituting 5- and 6-methoxycarbonyl-2-methylbenzimidazole, prepared as in Example 168, for 5- and 6-chloro-2-methylbenzimidazole in step 3. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.87 (bs, 4H), 1.87 (bs, 4H), 2.58 (s, 3H), 2.58 (s, 3H), 3.37 (s, 3H), 3.37 (s, 3H), 3.51 (bs, 4H), 3.51 (bs, 4H), 3.84 (s, 3H), 3.86 (s, 3H), 5.66 (s, 2H), 5.74 (s, 2H), 7.24 (d, 2H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 8.6 Hz), 7.67 (d, 1H, J = 8.4 Hz), 7.82-7.84 (m, 3H), 7.82-7.84 (m, 3H),

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7.98 (d, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.14 (s, 1H), 8.18 (s, 1H), 8.18 (s, 1H), 8.19 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 579 (M+H)<sup>+</sup>, 390, 280, 191. Anal calcd for C<sub>33</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub> · 0.6 H<sub>2</sub>O: C, 66.43; H, 5.40; N, 9.39. Found: C, 66.45; H, 5.39; N, 9.39.

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**Example 170**

Preparation of 1-(Pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1H-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared as a mixture of methyl regioisomers according to the method of Example 169, except substituting 5- and 6-methyl-2-methylbenzimidole, prepared as in Example 163, step 1, for 5- and 6-methoxycarbonyl-2-methylbenzimidazole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.86 (bs, 2H), 1.86 (bs, 2H), 2.40 (s, 3H), 2.50 (s, 3H), 3.31 (s, 3H), 3.47 (s, 3H), 3.51 (bs, 2H), 3.51 (bs, 2H), 5.56 (s, 2H), 5.56 (s, 2H), 6.99 (d, 1H, J = 8.4 Hz), 6.99 (d, 1H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.28 (s, 1H), 7.34 (d, 1H, J = 8.4 Hz), 7.36 (s, 1H), 7.43 (t, 1H, J = 8.0 Hz), 7.43 (t, 1H, J = 8.0 Hz), 7.43 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz), 7.98 (d, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.18 (s, 1H), 8.19 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 535 (M+H)<sup>+</sup>, 390. Anal calcd for C<sub>32</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> · 0.6 H<sub>2</sub>O · 0.2 Ac<sub>2</sub>O: C, 69.99; H, 5.87; N, 9.95. Found: C, 69.92; H, 5.79; N, 9.88.

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**Example 171**

Preparation of 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3H-2, 4, 6-trimethylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

Step 1: 1-N,N-Dimethylcarbamoyl-4-methoxycarbonyl-3-(4-aminomethylbenzoyl)indole.

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The desired compound was prepared according to the method of Example 102, steps 1-3, except substituting 4-methoxycarbonylindole, prepared as in Example 43, step 1, for 4-bromoindole.

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Step 2: 1-N,N-Dimethylcarbamoyl-4-bromo-3-(4-(N-3-nitro-2,6-dimethylpyridin-4-yl)aminomethylbenzoyl)indole.

A mixture of 1-N,N-dimethylcarbamoyl-4-methoxycarbonyl-3-(4-aminomethylbenzoyl)indole (150 mg, 0.393 mmol), triethylamine (60.1 μL, 0.432 mmol), and 3-nitro-4-chloro-2,6-dimethylpyridine (110 mg, 0.589 mmol) in THF (5 mL) was heated at 60 °C for 160 hours. The reaction mixture was cooled to ambient

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temperature and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (ethyl acetate) to give 128 mg of 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-(*N*-3-nitro-2,6-dimethylpyridin-4-yl)aminomethylbenzoyl)indole.

5    Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3H-2,4,6-trimethylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 57, step 8, except substituting 1-*N,N*-dimethylcarbamoyl-4-bromo-3-(4-(*N*-3-nitro-2,6-dimethylpyridin-4-yl)aminomethylbenzoyl)indole, prepared as in step 2, for 3-[(4-(*N*-3-nitropyrid-4-yl)aminomethyl)phenylsulfonyl]indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.47 (s, 3H), 2.51 (s, 3H), 2.62 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.56 (s, 2H), 7.22 (s, 1H), 7.24 (d, 2H, J = 8.4 Hz), 7.45 (t, 1H, J = 8.6 Hz), 7.56 (dd, 1H, J = 8.6, 1.5 Hz), 7.83 (d, 2H, J = 8.4 Hz), 7.87 (1H, dd, J = 8.6, 1.5 Hz), 8.11 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 584 (M+H+HOAc)<sup>+</sup>, 524 (M+H)<sup>+</sup>, 453, 364.

10    Anal calcd for C<sub>30</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> · 0.4 H<sub>2</sub>O · 0.4 HOAc: C, 65.93; H, 5.63; N, 12.48.

15    Found: C, 65.86; H, 5.61; N, 12.38.

### Example 172

20    Preparation of 1-(Pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1H-5-trifluoromethyl-2-methylmethylbenzimidazolyl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 171, except substituting 4-chloro-3-nitrobenzotrifluoride for 3-nitro-4-chloro-2,6-dimethylpyridine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.68 (s, 2H), 7.28 (d, 2H, J = 8.7 Hz), 7.45 (dd, 1H, J = 7.6, 8.8

25    Hz), 7.53 (dd, 1H, J = 1.6, 9.0 Hz), 7.57 (dd, 1H, J = 1.8, 7.6 Hz), 7.73 (d, 1H, J = 9.0 Hz), 7.83 (d, 2H, J = 8.7 Hz), 7.86 (dd, J = 1.6, 8.7 Hz), 7.93 (s, 1H), 8.10 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 563 (M+H)<sup>+</sup>, 364, 278, 201.

### Example 173

30    Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a 0 °C solution in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (25 mg, 0.045 mmol), prepared as in Example 44, was

35    added 3-chloroperbenzoic acid (80%, 12.5 mg, 0.045 mmol). The reaction mixture was stirred for 1 hour at 0 °C and then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated

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aqueous NaHCO<sub>3</sub>/NaHSO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Pure 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole was obtained by HPLC (20-40% CH<sub>3</sub>CN/H<sub>2</sub>O). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.55 (s, 3H),  
5 3.02 (s, 6H), 3.48 (s, 3H), 5.65 (s, 2H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 8.0 Hz), 7.85 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 7.6 Hz), 8.11 (s, 1H), 8.12 (dd, 1H, *J* = 7.6, 2.2 Hz), 8.68 (d, 1H, *J* = 2.2 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 512 (M+H)<sup>+</sup>, 496, 364.

10

**Example 174**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(4-chloro-1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

A mixture of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (60 mg), prepared as in  
15 Example 173, and POCl<sub>3</sub> (1 mL) was heated at 100 °C for 1 hour. The reaction mixture was cooled to ambient temperature and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (2% methanol/CH<sub>2</sub>Cl<sub>2</sub>) to give 1-*N,N*-  
20 dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(4-chloro-1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (34 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 2.60 (s, 3H), 3.01 (s, 6H), 3.47 (s, 3H), 5.68 (s, 2H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.45 (t, 1H, *J* = 8.6 Hz), 7.57 (d, 1H, *J* = 8.6 Hz), 7.68 (d, 1H, *J* = 6.0 Hz), 7.84 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 8.6 Hz), 8.11 (s, 1H), 8.12 (d, 1H, *J* = 6.0  
25 Hz). MS (DCI/NH<sub>3</sub>) *m/e* 530 (M+H)<sup>+</sup>, 364. Anal calcd for C<sub>28</sub>H<sub>24</sub>ClN<sub>4</sub>O<sub>5</sub> · 0.5 H<sub>2</sub>O · 0.375 HCl: C, 61.28; H, 4.74; N, 12.29. Found: C, 61.29; H, 4.67; N, 12.29.

**Example 175**

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1,5-H-2-methylimidazo[4.5-*c*]pyrid-4-one-1-yl)methyl]benzoyl}indole.

A mixture of 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole (61 mg), prepared as in Example 173, acetic anhydride (1 mL) was heated at 130 °C for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue  
35 was purified by chromatography on silica gel (5%, then 8% methanol/CH<sub>2</sub>Cl<sub>2</sub>) to give 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1,5-H-2-methylimidazo[4.5-

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c]pyrid-4-one-1-yl)methyl]benzoyl}indole (42 mg).  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  2.42 (s, 3H), 3.03 (s, 6H), 3.49 (s, 3H), 5.51 (s, 2H), 6.57 (d, 1H,  $J = 6.7$  Hz), 7.13 (t, 1H,  $J = 6.7$  Hz), 7.24 (d, 2H,  $J = 8.4$  Hz), 7.46 (t, 1H,  $J = 8.6$  Hz), 7.57 (d, 1H,  $J = 8.6$  Hz), 7.86 (d, 2H,  $J = 8.4$  Hz), 7.87 (d, 1H,  $J = 8.6$  Hz), 8.12 (s, 1H), 11.14 (d, 1H,  $J = 6.7$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  512 ( $\text{M}+\text{H}$ ) $^+$ , 441, 365, 264, 250, 236, 178.

### Example 176

#### Preparation of 1-*N,N*-Dimethylcarbamoyl-4-ethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

To a solution in DMF (4 mL) of 1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid (200 mg, 0.42 mmol), prepared as in Example 118 was added  $\text{NaHCO}_3$  (70 mg, 0.83 mmol) and bromoethane (62  $\mu\text{L}$ , 0.83 mmol). The reaction vessel was sealed and heated at 40  $^\circ\text{C}$  for 1.5 hours. The reaction mixture was cooled to ambient temperature and partitioned between  $\text{CH}_2\text{Cl}_2$  and brine. The aqueous phase was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5%, then 15% methanol/ $\text{CH}_2\text{Cl}_2$ ) to give 1-*N,N*-dimethylcarbamoyl-4-ethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole (53 mg).  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  0.92 (t, 3H,  $J = 7.4$  Hz), 2.57 (s, 3H), 3.02 (s, 6H), 3.95 (q, 2H,  $J = 7.0$  Hz), 5.65 (s, 2H), 7.30 (d, 2H,  $J = 7.8$  Hz), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 2H), 7.87 (d, 2H,  $J = 8.1$  Hz), 7.8-7.9 (m, 1H), 8.10 (s, 1H), 8.30 (d, 1H,  $J = 5.7$  Hz), 8.86 (s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  572 ( $\text{M}+\text{H}$ ) $^+$ . Anal calcd for  $\text{C}_{29}\text{H}_{27}\text{N}_5\text{O}_4 \cdot 0.3 \text{ Et}_2\text{O} \cdot 0.5 \text{ H}_2\text{O}$ : C, 66.41; H, 5.83; N, 12.82. Found: C, 66.42; H, 5.59; N, 12.66.

### Example 177

#### Preparation of 1-*N,N*-Dimethylcarbamoyl-4-(2-propyloxycarbonyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole.

##### Step 1: 4-(2-propyloxycarbonyl)indole.

The desired compound was prepared according to the method of Example 176, except substituting indole-4-carboxylic acid for 1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid, and substituting 2-bromopropane for bromoethane.

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Step 2: 1-*N,N*-Dimethylcarbamoyl-4-(2-propyloxy carbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 109, except substituting 4-(2-propyloxy carbonyl)indole, prepared as in step 1, for 4-chloroindole. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.02 (d, 6H, *J* = 6.3 Hz), 2.57 (s, 3H), 3.02 (s, 6H), 4.86 (apparent quint, 1H, *J* = 6.3 Hz), 5.64 (s, 2H), 7.30 (d, 2H, *J* = 8.1 Hz), 7.4-7.5 (m, 1H), 7.54-7.64 (m, 2H), 7.8-7.9 (m, 3H), 8.08 (s, 1H), 8.30 (d, *J* = 5.7 Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 524 (M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> · 1.2 H<sub>2</sub>O: C, 66.09; H, 5.80; N, 12.85. Found: C, 66.31; H, 5.57; N, 12.47.

### Example 178

Preparation of 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole.

Step 1: 1*H*-2-Methylnaphtho[2,3-*d*]imidazole.

The desired compound was prepared according to the method of Example 158, step 2, except substituting 2,3-diaminonaphthalene for 5-chloro-1,2-phenylenediamine.

Step 2: 4-Methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of Example 90, except substituting 4-methoxycarbonylindole, prepared as in Example 43, step 1, for 4,7-dimethoxycarbonylindole, and substituting 1*H*-2-methylnaphtho[2,3-*d*]imidazole, prepared as in step 1, for 1*H*-2-methylimidazo[4.5-*c*]pyridine.

Step 3: 1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole.

To a 0 °C solution in THF (5 mL) of 4-methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole (38 mg, 0.098 mmol), prepared as in step 2, was added NaH (95%, 3.00 mg, 0.118 mmol). After 10 minutes, dimethylcarbamyl chloride (11.5 μL, 0.137 mmol) was added and the reaction mixture was stirred for 15 minutes, then the cold bath was removed and stirring was continued for 15 minutes. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>, then 5% methanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 1-*N,N*-

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dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylnaphtho[2,3-d]imidazol-1-yl)methyl]benzoyl}indole (21 mg) as an amorphous solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.64 (s, 3H), 3.02 (s, 6H), 3.45 (s, 3H), 5.70 (s, 2H), 7.30 (d, 2H, J = 9 Hz), 7.35-7.44 (m, 3H), 7.55 (d, 1H, J = 7 Hz), 7.84 (d, 3H, J = 9 Hz), 7.90-8.05 (m, 3H), 8.10 (d, 2H, J = 7 Hz). MS (DCI/NH<sub>3</sub>) m/e 545 (M<sup>+</sup>). Anal calcd for C<sub>33</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O: C, 71.59; H, 5.28; N, 10.12. Found: C, 71.32; H, 5.36; N, 9.70.

### Example 179

10 Preparation of 1-N,N-dimethylcarbamoyl-4-(N,N-dimethylaminocarbonyloxy)-3-{3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of example 96, steps 1, 2, 3, and 4, except substituting 4-(N,N-dimethylaminocarbonyloxy)indole for 4,7-dimethoxycarbonylindole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.59 (s, 3H), 2.73 (s, 3H), 2.91 (s, 3H), 3.00 (s, 6H), 5.69 (s, 2H), 6.97-7.00 (d, 1H, J=8.8Hz), 7.13 (t, 1H), 7.33-7.38 (t, 1H, J=8.5Hz), 7.49-7.52 (d, 1H, J=8.1Hz), 7.59-7.67 (m, 3H), 8.02 (s, 1H), 8.29-8.31 (d, 1H, J=8.0Hz), 8.86 (s, 1H). MS (DCI/NH<sub>3</sub>) m/z = 543(M+1)<sup>+</sup>. Anal calcd for C<sub>29</sub>H<sub>27</sub>FO<sub>4</sub>N<sub>6</sub>: C, 63.14; H, 5.11; N, 15.23. Found C, 63.01; H, 5.39; N, 13.75.

### Example 180

Preparation of 1-N,N-dimethylcarbamoyl-4-ethynyl-3-{3-fluoro-4-[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

25

Step 1: 1-N,N-dimethylcarbamoyl-4-bromo-3-{3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to the method of example 96, steps 1, 2, 3, and 4, except substituting 4-bromoindole for 4,7-dimethoxycarbonylindole.

30

Step 2: 1-N,N-dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{3-fluoro-4-[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to example 106 except substituting 1-N,N-dimethylcarbamoyl-4-bromo-3-{3-fluoro-4-

35



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[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole for 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

5 Step 3: 1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{3-fluoro-4-

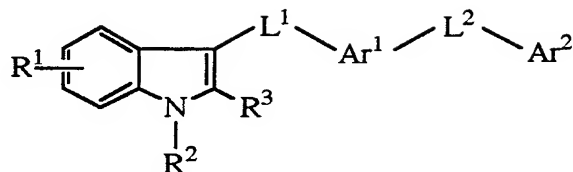
[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole.

The desired compound was prepared according to example 107 except substituting 1-*N,N*-dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{3-fluoro-4-[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole for 1-*N,N*-  
10 dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{4-[(1H-2-methylimidazo-[4,5-c]pyrid-1-yl)methyl]benzoyl}indole. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz): δ 2.57 (s, 3H), 3.01 (s, 6H), 4.07 (s, 1H), 5.69 (s, 2H), 7.05-7.15 (m, 1H), 7.30-7.45 (m, 2H), 7.55-7.75 (m, 4H), 8.18 (s, 1H), 8.29 (d, J=5.7 Hz, 1H), 8.85 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 480 (M+1)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>22</sub>N<sub>5</sub>O<sub>2</sub>F•0.1 CH<sub>2</sub>Cl<sub>2</sub>: C, 69.16;  
15 H, 4.59; N, 14.35. Found: C, 69.28; H, 4.43; N, 13.79.

135

WE CLAIM:

1. A compound of formula



- 5 or a pharmaceutically acceptable salt thereof wherein
- R<sup>1</sup>** is one or more groups independently selected from the group consisting of
- hydrogen,
  - halogen,
  - hydroxy,
  - 10 cyano,
  - alkyl of one to six carbon atoms,
  - alkynyl of two to four carbon atoms,
  - alkoxy of one to six carbon atoms,
  - alkanoyl of one to seven carbon atoms,
  - 15 -COOR<sup>6</sup>, wherein R<sup>6</sup> is hydrogen, alkyl of one to ten carbon atoms, or phenylalkyl wherein the alkyl portion is of one to four carbon atoms,
  - unsubstituted phenyl,
  - phenyl, substituted with
  - 20 alkyl of one to six carbon atoms,
  - alkoxy of one to six carbon atoms,
  - halogen,
  - NR<sup>4</sup>R<sup>5</sup>, where R<sup>4</sup> and R<sup>5</sup> are independently selected from hydrogen and alkyl of one to six carbon atoms, or R<sup>4</sup>
  - 25 and R<sup>5</sup> together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring,
  - COOR<sup>6</sup>,
  - C(O)NR<sup>4</sup>R<sup>5</sup>, or
  - 30 -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,
  - C(O)NR<sup>4</sup>R<sup>5</sup>,
  - OC(O)NR<sup>4</sup>R<sup>5</sup>,

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-NHC(O)NR<sup>4</sup>R<sup>5</sup>,  
2- or 3-furyl,  
35 2- or 3-thienyl,  
2-, 4-, or 5-thiazolyl,  
2-, 3-, or 4-pyridyl,  
2-, or 4-pyrimidyl,  
phenylalkyl in which the alkyl portion is of one to six carbon atoms,  
40 phenylalkyl, in which the alkyl portion is of one to six carbon atoms  
and the phenyl moiety is substituted with  
halogen,  
alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms,  
45 unsubstituted benzyoyl,  
benzoyl substituted with  
halogen,  
alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms,  
50 unsubstituted phenoxy,  
phenoxy substituted with  
halogen,  
alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms,  
55 unsubstituted phenylalkyloxy, in which the alkyl portion is of one to  
six carbon atoms,  
phenylalkyloxy in which the alkyl portion is of one to six carbon  
atoms and the phenyl moiety is substituted with  
halogen,  
60 alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms, and  
unsubstituted phenylalkanoyl, in which the alkanoyl portion is of one  
to seven carbon atoms,  
phenylalkanoyl, in which the alkanoyl portion is of one to seven  
65 carbon atoms and the phenyl moiety is substituted with;  
halogen,  
alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms;

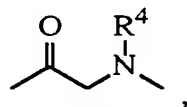
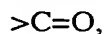
70 **R<sup>2</sup>** is selected from the group consisting of  
hydrogen,  
alkyl of one to six carbon atoms;  
-(CH<sub>2</sub>)<sub>p</sub>COOR<sup>6</sup>, where p 0, 1, 2, 3, or 4,  
-(CH<sub>2</sub>)<sub>q</sub>NR<sup>4</sup>R<sup>5</sup>, where q 2, 3, or 4,  
75 -(CH<sub>2</sub>)<sub>p</sub>COR<sup>6</sup>  
-(CH<sub>2</sub>)<sub>q</sub>OR<sup>6</sup>,  
-(CH<sub>2</sub>)<sub>p</sub>SO<sub>2</sub>R<sup>6</sup>,  
-(CH<sub>2</sub>)<sub>p</sub>SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,  
-(CH<sub>2</sub>)<sub>p</sub>CONR<sup>7</sup>R<sup>8</sup>, where R<sup>7</sup> and R<sup>8</sup> are independently selected from  
80 the group consisting of  
hydrogen,  
alkyl of one to six carbon atoms,  
-(CH<sub>2</sub>)<sub>r</sub>COOR<sup>6</sup>, where r is 1, 2, 3, or 4,  
-(CH<sub>2</sub>)<sub>r</sub>NR<sup>4</sup>R<sup>5</sup>,  
85 -(CH<sub>2</sub>)<sub>r</sub>OH,  
-(CH<sub>2</sub>)<sub>r</sub>SO<sub>2</sub>R<sup>6</sup>, and  
-(CH<sub>2</sub>)<sub>r</sub>SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,  
-(CH<sub>2</sub>)<sub>p</sub>CN  
-(CH<sub>2</sub>)<sub>p</sub>-1*H*-tetrazol-5-yl  
90 -CONHNH<sub>2</sub>, and;  
unsubstituted phenylalkyl wherein the alkyl portion is of one to four  
carbon atoms, and  
phenylakyl wherein the alkyl portion is of one to four carbon atoms  
and the phenyl moiety is substituted with  
95 halogen,  
alkyl of from one to six carbon atoms, or  
alkoxy of from one to six carbon atoms; or  
R<sup>7</sup> and R, taken together with the nitrogen atom to which they are  
attached, for a pyrrolidinyl or morpholinyl ring;

100

**R<sup>3</sup>** is selected from the group consisting of hydrogen and alkyl of one to six  
carbon atoms;

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105  $L^1$  is selected from the group consisting of



$>C=NNR^9R^{10}$ , where  $R^9$  and  $R^{10}$  are independently selected from  
hydrogen,

110 alkyl of one to six carbon atoms,

alkoxycarbonyl of from one to six carbon atoms,

aminocarbonyl,

alkylaminocarbonyl of one to six carbon atoms,

dialkylaminocarbonyl in which the alkyl groups are

115 independently of one to six carbon atoms,

alkanoyl of one to six carbon atoms,

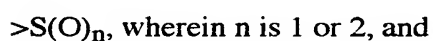
unsubstituted phenyl, and

phenyl substituted with

halogen,

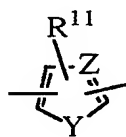
120 alkyl of from one to six carbon atoms, or

alkoxy of from one to six carbon atoms; and



125

$Ar^1$  is a valence bond or a radical of formula



where Y is O, S, or  $-CH=CH-$ , Z is N or CH, and  $R^{11}$  is selected  
from the group consisting of

130

hydrogen,

alkyl of one to six carbon atoms,

alkenyl of two to six carbon atoms,

alkoxy of one to six carbon atoms, and

135

halogen;

$L^2$  is selected from the group consisting of

a valence bond,

unsubstituted straight-chain alkylene of one to six carbon atoms,

140 straight-chain alkylene of one to six carbon atoms substituted with one

or more groups selected from

alkyl of one to six carbon atoms,

alkenyl of two to six carbon atoms,

alkoxycarbonyl of one to six carbon atoms,

145 alkoxy of one to six carbon atoms,

alkylthio of one to six carbon atoms,

alkoxyalkyl in which the two alkyl portions each are of

one to six carbon atoms,

alkylthioalkyl in which the alkoxy and alkyl portions

150 are independently of one to six carbon atoms,

unsubstituted phenylalkyl wherein the alkyl portion is of one to six carbon atoms,

phenylalkyl wherein the alkyl portion is of one to six carbon atoms, and the phenyl ring is substituted with

155 alkyl of one to six carbon atoms,

haloalkyl of one to six carbon atoms,

alkoxy of one to six carbon atoms,

hydroxy, or

halogen,

160 unsubstituted thiophenyl, and

thiophenyl substituted with

alkyl of one to six carbon atoms,

haloalkyl of one to six carbon atoms,

alkoxy of one to six carbon atoms,

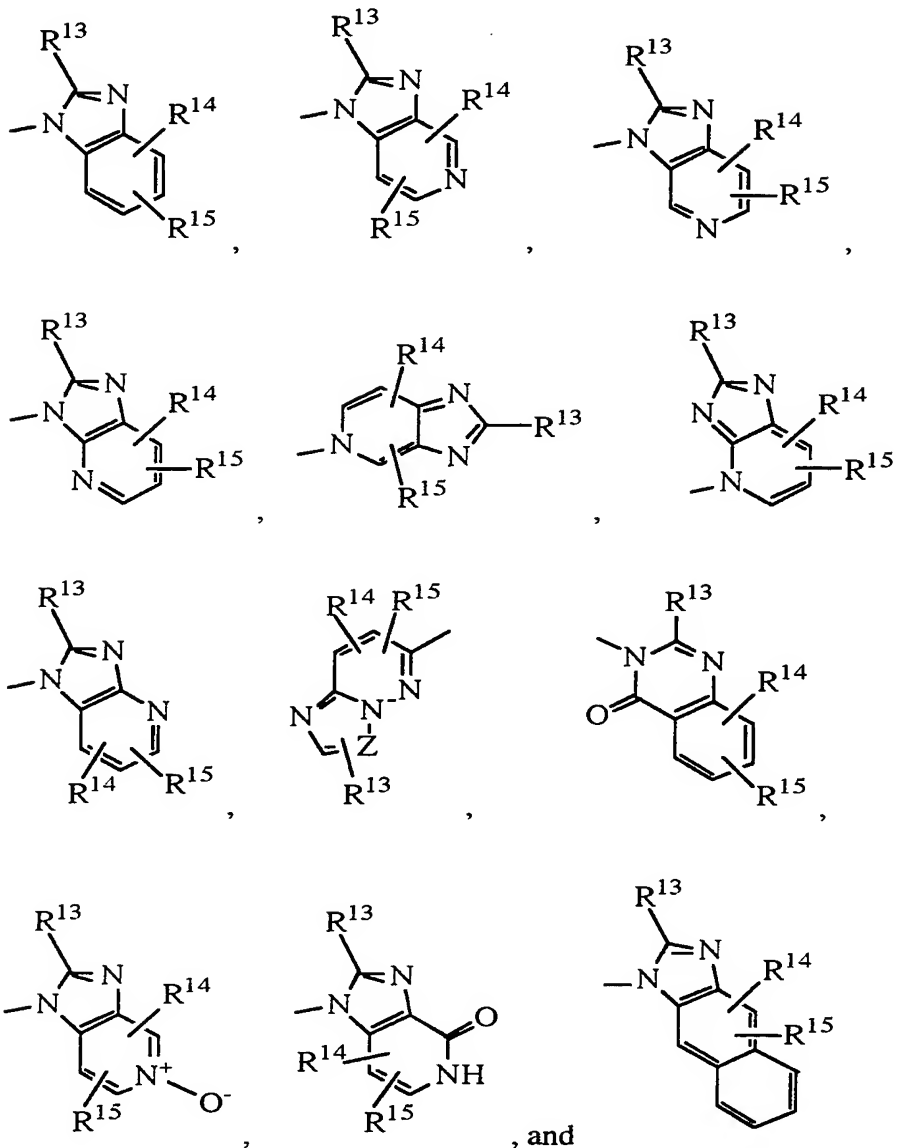
165 hydroxy, or

halogen,

with the proviso that  $L^2$  is unsubstituted alkylene or alkylene substituted alkyl when  $Ar^1$  is a valence bond;

140

170

 $\text{Ar}^2$  is selected from the group consisting of

175

180

where R<sup>13</sup> is selected from the group consisting of

alkyl of one to six carbon atoms,

alkenyl of two to six carbon atoms,

alkoxy of one to six carbon atoms,

alkylthio of one to six carbon atoms,

185

alkoxyalkyl in which the alkoxy and alkyl portions are independently of one to six carbon atoms,

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alkylthioalkyl in which the alkyl portions each independently of one to six carbon atoms,

haloalkyl of one to six carbon atoms,

190 unsubstituted phenylalkyl wherein the alkyl portion is of one to six carbon atoms,

phenylalkyl wherein the alkyl portion is of one to six carbon atoms and the phenyl is substituted with

alkyl of one to six carbon atoms,

195 haloalkyl of one to six carbon atoms,

alkoxy of one to six carbon atoms,

hydroxy, or

halogen,

cycloalkyl of three to eight carbon atoms,

200 unsubstituted thiophenyl, and

thiophenyl substituted with

alkyl of one to six carbon atoms,

haloalkyl of one to six carbon atoms,

alkoxy of one to six carbon atoms,

205 hydroxy, or

halogen, and

R<sup>14</sup> and R<sup>15</sup> are independently selected from the group consisting of hydrogen,

alkyl of one to six carbon atoms,

210 alkenyl of two to six carbon atoms,

halogen,

cyano,

carboxyl,

alkoxycarbonyl of two to six carbon atoms,

215 aminocarbonyl,

alkylaminocarbonyl of two to six carbon atoms,

dialkylaminocarbonyl in which the alkyl groups are independently of one to six carbon atoms,

alkanoyl,

220 hydroxyalkyl,

haloalkyl,

alkoxy of one to six carbon atoms,



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alkylthio of one to six carbon atoms,  
alkylsulfinyl of one to six carbon atoms,  
225 alkylsulfonyl of one to six carbon atoms,  
amino,  
alkonylamino, of one to six carbon atoms, and  
nitro, or

230  $R^{14}$  and  $R^{15}$ , together with the carbon atoms to which they are  
attached define a phenyl ring or 5- to 7-membered  
cycloalkylene ring.

2. A compound as defined by Claim 1, or the pharmaceutically acceptable salt thereof wherein

$R^1$  is one or more groups independently selected from the group consisting of

5 hydrogen,  
halogen,  
alkyl of one to six carbon atoms,  
alkynyl of two to four carbon atoms,  
alkoxy of one to six carbon atoms,  
10  $-COOR^6$ , wherein  $R^6$  is hydrogen, alkyl of one to ten carbon atoms, or  
phenylalkyl wherein the alkyl portion is of one to four carbon  
atoms,  
 $-OC(O)NR^4R^5$ , wherein  $R^4$  and  $R^5$  are independently selected from  
15 hydrogen and alkyl of one to six carbon atoms, or  $R^4$  and  $R^5$   
together with the nitrogen atom to which they are attached form  
a pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring,  
phenyl,  
phenyl, optionally substituted with  
20 alkyl of one to six carbon atoms,  
alkoxy of one to six carbon atoms, or  
halogen,  
phenylalkyl wherein the alkyl portion is of one to four carbon  
atoms,

25

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phenylalkyl wherein the alkyl portion is of one to four carbon atoms, and the phenyl moiety is substituted with

halogen,

30

alkyl of one to six carbon atoms, or

alkoxy of one to six carbon atoms,

phenoxy, and

phenoxy substituted with

halogen,

35

alkyl of one to six carbon atoms, or

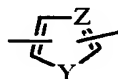
alkoxy of one to six carbon atoms;

**R<sup>3</sup>** is hydrogen;

40

**L<sup>1</sup>** is  $>C=O$  or  $-SO_2-$ ;

**Ar<sup>1</sup>** is



wherein

45

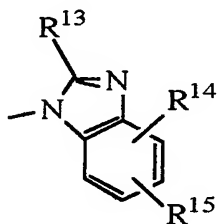
Y is O, S, or  $-CH=CH-$ ,

Z is N or CH;

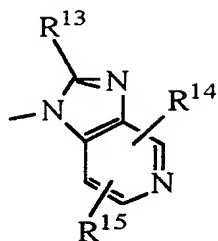
**L<sup>2</sup>** is straight chain alkylene of one to six carbon atoms; and

50

**Ar<sup>2</sup>** is selected from the group consisting of

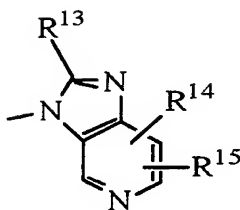


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, and

55



wherein R<sup>13</sup> is methyl and R<sup>14</sup> and R<sup>15</sup> are hydrogen.

60

3. A compound as defined by Claim 2, or the pharmaceutically acceptable salt thereof wherein Ar<sup>1</sup> is selected from the group consisting of unsubstituted phenyl and phenyl substituted with

5

alkyl of one to six carbon atoms,  
alkoxy of one to six carbon atoms, or  
halogen.

4. A compound as defined by Claim 3, or the pharmaceutically acceptable salt thereof wherein

R<sup>1</sup> is one or more groups independently selected from the group consisting of

5

hydrogen,  
alkyl of one to six carbon atoms,  
alkynyl of two to four carbon atoms,  
-COOR<sup>6</sup>, wherein R<sup>6</sup> is hydrogen, alkyl of one to ten carbon atoms, or  
phenylalkyl wherein the alkyl portion is of one to four carbon  
atoms,

10

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15 -OC(O)NR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from hydrogen and alkyl of one to six carbon atoms, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring, phenylmethyl, 4-fluorophenyl, and 4-fluorophenoxy;

20

R<sup>2</sup> is -C(O)N(CH<sub>3</sub>)<sub>2</sub> or -(CH<sub>2</sub>)<sub>q</sub>OR<sup>6</sup> where q is 1, 2, 3, or 4, and

L<sup>1</sup> is >C=O or -SO<sub>2</sub>-.

5. A compound as defined by Claim 4, or the pharmaceutically acceptable salt thereof wherein L<sup>2</sup> is methylene.
6. A compound as defined by Claim 4, or the pharmaceutically acceptable salt thereof wherein L<sup>2</sup> is a valence bond.
7. A compound as defined by Claim 4, or the pharmaceutically acceptable salt thereof wherein Ar<sup>1</sup> is a valence bond.
8. A compound as defined by Claim 1 selected from the group consisting of:  
 6-(4-fluorophenyl)-3-{4-[(1H-2-ethylbenzimidazolyl)methyl]benzoyl}indole,  
 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylbenzimidazolyl)methyl]benzoyl}indole,  
 5 6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
 10 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole hydrochloride,  
 6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,  
 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,

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- 15 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,  
6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4.5-c]pyridyl)benzoyl]indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[4-(1H-2-methylimidazo[4.5-c]pyrid-1-yl)benzoyl]indole,
- 20 6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,
- 25 1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-[4-(5H-2-methylimidazo[4.5-c]pyrid-5-ylmethyl)benzoyl]indole,
- 30 3-{3-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
3-{3-[(3H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{3-[(3H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,
- 35 3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole,
- 40 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-[(3H-2-methylimidazo[4.5-c]pyrid-3-yl)methylcarbonyl]indole,
- 45 1-*N,N*-dimethylcarbamoyl-3-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(3H-2-methylimidazo[4.5-b]pyrid-3-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-b]pyrid-1-yl)methyl]benzoyl}indole,
- 50

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- 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-trifluoromethylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-imidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
55 1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-(2-propyl)imidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-phenylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[1H-2-ethylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
60 3-{3-[(5H-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{3-[(5H-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl}benzoyl}indole,  
1-*p*-toluenesulfonyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-*c*]pyridyl)methyl}benzoyl}indole,  
65 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(3H-2-methylimidazo[4.5-*c*]pyrid-3-yl)pent-5-ylcarbonyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)pent-5-ylcarbonyl}indole,  
70 1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-[(5H-2-methylimidazo[4.5-*c*]pyrid-5-yl)pent-5-ylcarbonyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(3H-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenoxy)-3-{4-[(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
75 1-*N,N*-dimethylcarbamoyl-6-phenylmethyl-3-{4-[(3H-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-phenylmethyl-3-{4-[(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
80 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3H-2-methylimidazo[4.5-*c*]pyrid-3-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl}benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-3-{4-[(1H-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl}phenylsulfonyl}indole,  
85

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- 1-(morpholin-4-ylcarbonyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
1-(*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyridyl)methyl]benzoyl}indole,  
90 4,7-dimethoxycarbonyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
4,7-dimethyl-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
4,7-dimethyl-3-{4-[(3H-2-methylimidazo[4,5-c]pyrid-3-yl)methyl]benzoyl}indole,  
95 7-benzyloxy-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
7-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
100 6-(4-fluorophenyl)-3-{*N*-[3-(1H-2-methylimidazo[4.5-c]pyrid-1-yl)propyl]sarcosyl}indole-1-carboxylic acid dimethyl amide,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-benzyloxy-3-{4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl}indole,  
105 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{5-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]thien-2-oyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylaminocarbonyl}indole  
hydrochloride,  
110 1-*N,N*-dimethylcarbamoyl-5-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]phenylsulfonyl}indole,  
115 1-*N,N*-dimethylcarbamoyl-4-bromo-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-acetyl-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(fur-2-yl)-3-{4-[(1H-2-methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
120

- 1-*N,N*-dimethylcarbamoyl-4-(benzo[b]fur-2-yl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(trimethylsilylethynyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
125 1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
4-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
130 1-*N,N*-dimethylcarbamoyl-4-fluoro-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-2-methyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
135 1,4-di-*N,N*-dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-5-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
140 4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
4-methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-benzyloxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
145 1-*N,N*-dimethylcarbamoyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic acid,  
1-*N,N*-dimethylcarbamoyl-4-(*N*-nonylcarbamoyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
150 1-*N,N*-dimethylcarbamoyl-4-(dec-1-yloxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
155 1-*N,N*-dimethylcarbamoyl-4-methyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,



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- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)hex-6-ylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-  
methylbenzimidazolyl)methyl]benzoyl}indole,  
160 4-methoxycarbonyl-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1*H*-2-  
methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)pent-5-ylcarbonyl]indole,  
165 1-*N,N*-dimethylcarbamoylmethyl-4-methoxycarbonyl-3-[(1*H*-2-  
methylimidazo[4.5-c]pyrid-1-yl)pent-5-ylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)pent-5-ylcarbonyl]indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(2-methyl-4-  
170 (3*H*)quinazolinone-3-yl)methyl]benzoyl}indole,  
1-(2-ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylsulfamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-  
methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
175 1-*N,N*-dimethylsulfamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-  
methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-acetoxymethyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-c]pyrid-  
1-yl)methyl]benzoyl}indole,  
1-(2-propanesulfonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-  
180 c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(1-pinacolyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-c]pyrid-  
1-yl)methyl]benzoyl}indole,  
1-carbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-c]pyrid-1-  
yl)methyl]benzoyl}indole,  
185 1-*N*-methylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-  
c]pyrid-1-yl)methyl]benzoyl}indole,  
1-(2-ethoxyethyl)-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-c]pyrid-1-  
yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(1*H*-2-  
190 methylimidazo[4.5-c]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{3-methoxy-4-[(3*H*-2-  
methylimidazo[4.5-c]pyrid-3-yl)methyl]benzoyl}indole,

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- 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole,  
195 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]phenylsulfonyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-hydroxy-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
200 1-*N,N*-dimethylcarbamoyl-6-bromo-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-6-(benzo[*b*]fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
205 1-*N,N*-dimethylcarbamoyl-6-(fur-2-yl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonylamino)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
210 1-*N,N*-dimethylcarbamoyl-4-cyano-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzyl}indole,  
215 1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2-methylimidazo[4.5-*b*]pyrid-3-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*b*]pyrid-1-yl)methyl]benzoyl}indole,  
220 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5*H*-2-methylimidazo[4.5-*c*]pyrid-5-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)eth-1-yl]benzoyl}indole,  
225 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[1-(1*H*-imidazo[4.5-*c*]pyrid-1-yl)eth-1-yl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,

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- 230 1-*N,N*-dimethylcarbamoyl-4-chloro-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,  
1-(2-ethoxyethyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,  
1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5-, and 6-chlorobenzimidazolyl)methyl]benzoyl}indole,
- 235 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-(trifluoromethyl)benzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-4- and 7-methylbenzimidazolyl)methyl]benzoyl}indole,
- 240 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-nitrobenzimidazolyl)methyl]benzoyl}indole,
- 245 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5, 6-dichlorobenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole,  
1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methoxycarbonylbenzimidazolyl)methyl]benzoyl}indole,
- 250 1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-2-methyl-5- and 6-methylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(3*H*-2, 4, 6-trimethylimidazo[4.5-*c*]pyrid-3-yl)methyl]benzoyl}indole,
- 255 1-(pyrrolidin-1-ylcarbonyl)-4-methoxycarbonyl-3-{4-[(1*H*-5-trifluoromethyl-2-methylmethylbenzimidazolyl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(5-oxide-1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(4-chloro-1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,
- 260 1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1,5-*H*-2-methylimidazo[4.5-*c*]pyrid-4-one-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole,

- 265 1-*N,N*-dimethylcarbamoyl-4-(2-propyloxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, and  
1-*N,N*-dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylnaphtho[2,3-*d*]imidazol-1-yl)methyl]benzoyl}indole.
9. A compound or pharmaceutically acceptable salt thereof selected from the group consisting of  
1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
5 1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole,  
1-*N,N*-dimethylcarbamoyl-4-(*N,N*-dimethylaminocarbonyloxy)-3-{4-  
10 [(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole, and  
1-*N,N*-Dimethylcarbamoyl-4-methoxycarbonyl-3-{4-[(1*H*-2-methylimidazo[4.5-*c*]pyrid-1-yl)methyl]benzoyl}indole.
10. A pharmaceutical composition useful for inhibiting PAF in a mammal in need of such treatment comprising a PAF-inhibitive effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.
- 5
11. A method of treating PAF-mediated disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 1.

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 94/14112

## A. CLASSIFICATION OF SUBJECT MATTER

C 07 D 471/04, C 07 D 403/10, C 07 D 405/14,  
C 07 D 409/14, C 07 D 413/14, C 07 D 417/14,

According to International Patent Classification (IPC) or to both national classification and IPC 6

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C 07 D, A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 93/01 813 (ABBOTT) 04 February 1993 (04.02.93), claims 1,5-7 (cited in the application). --	1, 10, 11
A	DE, A, 2 427 207 (CIBA-GEIGY) 09 January 1975 (09.01.75), claims 1,43,50. --	1, 10
A	EP, A, 0 171 037 (STERLING DRUG) 12 February 1986 (12.02.86), claims 1,10. --	1, 10
A	DE, A, 3 200 705 (AGFA-GEVAERT) 21 July 1983 (21.07.83),	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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\*&amp;\* document member of the same patent family

Date of the actual completion of the international search  
15 February 1995

Date of mailing of the international search report

- 6. 03. 95

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## INTERNATIONAL SEARCH REPORT

-2-

International Application No  
PCT/US 94/14112

## A. CLASSIFICATION OF SUBJECT MATTER

C 07 D 487/04, A 61 K 31/435, A 61 K 31/50  
According to International Patent Classification (IPC) or to both national classification and IPC 6

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>page 44, line 7. --</p> <p>EP, A, 0 444 451 (STERLING DRUG) 04 September 1991 (04.09.91), claim 1; formula VII. --</p>	1
A	<p>CHEMICAL ABSTRACTS, vol. 113, no. 1, issued 1990, July 02, (Columbus, Ohio, USA), FUJISAWA PHARMACEUTICAL CO., LTD. "Preparation of imida- zolidine derivatives as platelet activating factor (PAF) antagonists", page 618, no. 6 344p; &amp; JP, A, 02 015 068. --</p>	1, 10

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\* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search  
15 February 1995

Date of mailing of the international search report

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Fax (+ 31-70) 340-3016

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>---            CHEMICAL ABSTRACTS, vol. 96,            no. 14, issued 1982, April 05            (Columbus, Ohio, USA),            Nagarajan, K. et al.            "Structure-activity relations            among cyclic and acyclic            S-(3-indolyl) isothioureas -            development of a potent            vasoconstrictor, tinazoline,            3-(2-imidazolin-2-yl-thio)            indole",            page 20, no.115 505t;            &amp; Indian J. Exp. Biol. 1981,            19(12), 1150-3 (Eng).</p>	1
A	<p>---            CHEMICAL ABSTRACTS, vol. 108,            no. 7, issued 1988,            February 15,            (Columbus, Ohio, USA),            HELBECQUE N. et al.            "Grossularine-1 and grossula-            rine-2, alpha-carbolines            from Dendrodoa grossularia,            as possible intercalative            agents",            page 16, no. 48 713k;            &amp; Cancer Biochem. Biophys.            1987, 9(3), 271-9 (Eng).</p>	1
A	<p>---            CHEMICAL ABSTRACTS, vol. 111,            no. 17, issued 1989,            October 23,            (Columbus, Ohio, USA),            MOQUIN-PATTEY, CAROLE et al.            "Grossularine-1 and grossula-            rine-2, cytotoxic            alpha-carbolines from the            tunicate Dendrodoa            grossularia",            page 440, no. 150 783p;            &amp; Tetrahedron 1989, 45(11),            3445-50 (Eng).</p>	1
A	<p>---            CHEMICAL ABSTRACTS, vol. 102,            no. 11, issued 1985, March 18            (Columbus, Ohio, USA),            MOQUIN, CAROLE et al.            "Grossularine, a novel indole            derivative from the marine            tunicate, Dendrodoa            grossularia",            page 360, no. 93 257b;</p>	1

## INTERNATIONAL SEARCH REPORT

-4-

International Application No

PCT/US 94/14112

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p data-bbox="488 317 972 380">&amp; Tetrahedron Lett. 1984, 25(44), 5047-8 (Eng). -----</p>	



## ANHANG

zum internationalen Recherchen-  
bericht über die internationale  
Patentanmeldung Nr.

## ANNEX

to the International Search  
Report to the International Patent  
Application No.

## ANNEXE

au rapport de recherche inter-  
national relatif à la demande de brevet  
international n°

PCT/US 94/14112 SAE 101584

In diesem Anhang sind die Mitglieder  
der Patentfamilien der im obenge-  
nannten internationalen Recherchenbericht  
angeführten Patentdokumente angegeben.  
Diese Angaben dienen nur zur Unter-  
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This Annex lists the patent family  
members relating to the patent documents  
cited in the above-mentioned inter-  
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La présente annexe indique les  
membres de la famille de brevets  
relatifs aux documents de brevets cités  
dans le rapport de recherche inter-  
national visée ci-dessus. Les renseigne-  
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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WD A1 9301813	04-02-93	AU A1 23391/92 AU B2 651243 CA A1 2112562 EP A1 595924 EP A4 595924 IL A0 102494 JP T2 6510027 PT A 100698	23-02-93 14-07-94 04-02-93 11-05-94 24-08-94 14-01-93 10-11-94 29-10-93
DE A1 2427207	09-01-75	AT A 4847/74 AT B 333267 BE A1 816262 CH A 574441 DD C 112132 DK A 3166/74 DK B 142701 DK C 142701 ES A1 427269 FR A1 2233047 FR B1 2233047 IE B 39495 IL A0 44876 IL A1 44876 JP A2 50035160 JP B4 58049557 LU A 70309 NL A 7407614 SE A 7407175 SE B 408709 SE C 408709 US A 3954757 US A 4055647 YU A 1647/74	15-03-76 10-11-76 13-12-74 15-04-76 20-03-75 17-02-75 22-12-80 21-09-81 01-07-76 10-01-75 04-11-77 25-10-78 31-07-74 31-01-78 03-04-75 05-11-83 13-04-76 17-12-74 16-12-74 02-07-79 11-10-79 04-05-76 25-10-77 31-08-82
EP A2 171037	12-02-86	AT E 77371 AU A1 45764/85 AU B2 574817 CA A1 1246563 CA A2 1255305 CA A2 1255312 CA A2 1255316 CA A2 1258069 CA A2 1258070 DE C0 3586224 DE T2 3586224 DK A0 3544/85 DK A 3544/85 EP A3 171037 EP B1 171037 ES A1 545894 ES A5 545894 ES A1 8609246 ES A1 552912 ES A5 552912 ES A1 552909 ES A1 552911 ES A1 552910 ES A5 552909 ES A5 552911 ES A1 8800149 ES A5 552910 ES A1 8800901 ES A1 8800902 ES A1 8801203	15-07-92 13-02-86 14-07-88 13-12-88 06-06-89 06-06-89 06-06-89 01-08-89 01-08-89 23-07-92 28-01-93 05-08-85 07-02-86 26-08-87 17-06-92 16-07-86 16-08-86 16-12-86 16-10-87 16-11-87 01-12-87 01-12-87 16-12-87 29-12-87 29-12-87 01-01-88 15-01-88 16-02-88 16-02-88 01-03-88

	FI	AO	852973	01-08-85
	FI	A	852973	07-02-86
	FI	A	893254	04-07-89
	FI	A	893254	04-07-89
	FI	A	893255	04-07-89
	FI	A	893256	04-07-89
	FI	A	893257	04-07-89
	FI	AO	893253	04-07-89
	FI	AO	893254	04-07-89
	FI	AO	893255	04-07-89
	FI	AO	893256	04-07-89
	FI	AO	893257	04-07-89
	GR	A	851937	05-12-85
	IE	B	57863	05-05-93
	IL	AO	75966	31-12-85
	IL	A1	75966	15-08-89
	JP	A2	61047463	07-03-86
	JP	B4	6070010	07-09-94
	KR	B1	8700548	18-03-87
	MX	A	160612	28-03-90
	NO	A	853066	07-02-86
	NO	A	903304	07-02-86
	NO	A	903305	07-02-86
	NO	A	903306	07-02-86
	NO	AO	903304	25-07-90
	NO	AO	903305	25-07-90
	NO	AO	903306	25-07-90
	NO	B	169067	27-01-92
	NO	C	169067	06-05-92
	NZ	A	212953	26-02-90
	NZ	A	225464	26-02-90
	NZ	A	225465	26-02-90
	NZ	A	225466	26-02-90
	NZ	A	225467	26-02-90
	PH	A	23498	16-08-89
	PT	A	80919	01-09-85
	PT	B	80919	30-09-87
	ZA	A	8505923	26-03-86
	US	A	4581354	08-04-86
	US	A	4634776	06-01-87
	US	E	32761	04-10-88
	US	A	4885295	05-12-89
	US	A	4978664	18-12-90
	US	A	5013732	07-05-91
-----				
DE	A1	3200705	21-07-83	
	GB	AO	8300702	16-02-83
	GB	A1	2128349	26-04-84
	GB	B2	2128349	29-08-85
	JP	A2	58123537	22-07-83
	US	A	4461827	24-07-84
-----				
EP	A2	444451	04-09-91	
	AU	A1	71222791	29-08-91
	AU	B2	638795	08-07-93
	CA	AA	2035711	27-08-91
	EP	A3	444451	08-04-92
	FI	AO	910851	22-02-91
	FI	A	910851	27-08-91
	HU	AO	910400	28-08-91
	HU	A2	56565	30-09-91
	HU	B	208132	30-08-93
	IL	AO	97313	25-05-92
	NO	AO	910731	25-02-91
	NO	A	910731	27-08-91
	NZ	A	237041	25-11-92
	PT	A	96871	31-10-91
	US	A	5068234	26-11-91
	US	A	5324737	28-06-94